FINAL REPORT

Development of an Environmental Fate Simulator for New and Proposed Military-unique Munition Compounds

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14. ABSTRACT

The objective of the proposed work is to develop an Environmental Fate Simulator (EFS) that will provide the managers of military training and testing ranges estimates of the vulnerability of these aquifers and surface waters to new and proposed energetic materials and their potential transformation products. During the evolution of this project, the name of the EFS was changed to the Chemical Transformation Simulator (CTS) to better convey the primary function of the simulator. Our working hypothesis is that there is a substantial amount of process science that has been published in the peer-reviewed literature concerning the transport and transformation of existing N-based munitions (e.g., TNT, 2,4-DNT and RDX) and related N-based chemicals (i.e., nitro aromatics, aromatic amines and substituted azobenzenes) that can be encoded through the use of cheminformatics applications. Consequently, this process science could then be applied to predicting the transport and transformation for emerging N-based munitions, for which little fate data exists.

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List of Acronyms:

D4EM	Data for Environmental Modeling
2,4DNT	Dinitrotoluenes
DOE	U.S. Department of Energy
CTS	Chemical Transformation Simulator
EFS	Environmental Fate Simulator
EPA	Environmental Protection Agency
EPI Suite	Estimation Programs Interface Suite
ERD	Ecosystems Research Division
ERDC	U.S. Army Engineer Research and Development Center
FRAMES	Framework for Risk Analysis in Multimedia Environmental System
^{15}N-NMR	Nitrogen Nuclear Magnetic Spectroscopy
NOM	Natural organic matter
OC/DOC	Organic Carbon/Dissolved Organic Carbon
ORD	Offices of Research and Development
PCP	Physicochemical Properties Calculator
PI	Principal Investigator
QSAR	Quantitative Structure Activity Relationship
RDX	1,3,5-hexahydrotrinitrotriazine
RPS	Reaction Pathway Simulator
SERDP	Strategic Environmental Research and Development Program
SPARC	SPARC Performs Automated Reasoning in Chemistry
TNT	Trinitrotoluene
2ADNT	2-amino-4,6-dinitrotoluene
4ADNT	4-amino-2,6-dinitrotoluene
2,4DANT	2,4-diamino-6-nitrotoluene
2,6DANT	2,6-diamino-4-nitrobenzene
2,4DNAN	2,4-dintroanisole
2A4NA	2-amino-4-nitroanisole
4A2NA	4-amino-2-nitroanisole
2,4DAA	2,4-diaminoanisole

Keywords

Environmental fate, transformation pathways, reduction, hydrolysis, physicochemical properties, and cheminformatics

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Development of an Environmental Fate Simulator for New and Proposed Military-unique Munition Compounds

Abstract

Objectives:

DoD is responsible for assessing the environmental exposure resulting from testing and training activities associated with military munitions. Of greatest concern is potential for off-site exposure to these materials and their degradation products, primarily as a result of movement through surface waters and underlying aquifers. Modeling systems and databases currently exist where the user is responsible for defining individual chemicals and their properties, which is necessary to conduct chemical exposure and risk assessments. These data are required input into for the U.S. Army Groundwater Modeling System (GMS), the Adaptive Risk Assessment Modeling System (ARAMS), and the Training Range Environmental Evaluation and Characterization System (TREECS). The objective of the proposed work is to develop an Environmental Fate Simulator (EFS) that will provide the managers of military training and testing ranges estimates of the vulnerability of these aquifers and surface waters to new and proposed energetic materials and their potential transformation products. During the evolution of this project the name of the EFS was changed to the Chemical Transformation Simulator (CTS) to better convey the primary function of the simulator. Our working hypothesis is that there is a substantial amount of process science that has been published in the peer-reviewed literature concerning the transport and transformation of existing N-based munitions (e.g., TNT, 2,4-DNT and RDX) and related N-based chemicals (i.e., nitro aromatics, aromatic amines and substituted azobenzenes) that can be encoded through the use of cheminformatics applications. Consequently, this process science could then be applied to predicting the transport and transformation for emerging N-based munitions, for which little fate data exists.

Technical Approach:

The primary focus of this project was the development of two major components of the CTS: the Physicochemical Properties Calculator (PPC) and the Reaction Pathway Simulator (RPS). The selection of calculators supporting the PPC was based on their accessibility and their ability to ensure complete coverage of the molecular descriptors required for fate modeling. Development of the RPS allowed for the encoding of the process science underlying the environmental fate of existing munitions. This process began with a thorough review of literature concerning the transformation pathways of the chemicals of interest, including existing N-based munitions and related N-based chemicals. The process science was then encoded with the use of Chemical Terms Language and Smart Reaction Smile Strings, which, based on chemical structure analysis, provides the dominant transformation products as a function of environmental conditions.

Results:

The result of this work is the development of the Chemical Transformation Simulator: A Cheminformatics-based Tool for Predicting Transformation Pathways and Physicochemical Properties. This is a web-based tool that runs on EPA's CGI cloud servers and will be fully accessible to DoD personnel. In addition to the PPC and the RPS, a chemical editor was incorporated that allows the user to enter the chemical(s) of interest by providing a chemical structure, SMILES string, CAS# or common name

The output of the RPS is based on the selection and execution of reaction libraries that represent one-step reactions for the transformation of reactive functional groups (e.g., reduction and hydrolysis). These one-step reactions represent viable transformation pathways based on the identification and subsequent transformation of reactive functional groups. The functional group transformations list extends beyond those typically found in N-based munitions. The expanded reaction libraries address other classes of chemicals (e.g., halogenated solvents) that are of interest to both the DOD and EPA. A reaction library for human metabolism for phase 1 biotransformations, developed by ChemAxon, is also available through the CTS. The PCP provides a consensus approach that allows the user to compare output generated by a number of calculators that take different approaches to calculating specific physicochemical properties. The calculators include: (1) SPARC (SPARC Performs Automated Reasoning in Chemistry), which uses a mechanistic-based approach; (2) EPI Suite, which uses a fragment-based approach; (3) TEST (Toxicity Estimation Software Tool), which uses QSAR-based approaches; and (4) ChemAxon plug-in calculators, which uses an atom-based fragment approach. The output derived from these calculators enables the user to compare the calculated data with measured data in readily accessible web-based databases.

Benefits:

Through the integration of the cheminformatics applications with software technologies, the CTS will be able to eventually provide seamless consumption by modeling toolsets for assessing environmental exposure and subsequent human/ecological receptor health risks associated with loading and fate/transport of residual energetic materials and their degradation products.

Objective

The objective of the proposed work is to develop a Chemical Transformation Simulator (CTS) that will provide the managers of military training and testing ranges estimates of the vulnerability of aquifers and surface waters to new and proposed energetic materials and their potential transformation products. Our working hypothesis is that there is a substantial amount of process science that has been published in the peer-reviewed literature concerning the transport and transformation of existing N-based munitions (e.g., TNT, 2,4-DNT and RDX) and related N-based chemicals (i.e., Nitro Aromatics, aromatic amines and substituted azobenzenes) that can be encoded through the use of cheminformatics applications. Consequently, this process science can then be applied to predicting the transport and transformation for emerging N-based munitions for which little fate data exists. The work will provide physicochemical properties of parent and predicted transformation products. Through the integration of the cheminformatics applications with software technologies, the CTS will be able to eventually provide seamless consumption by modeling toolsets for assessing environmental exposure and subsequent human/ecological receptor health risks associated with loading and fate/transport of residual energetic materials and their predicted degradation products.

This report is addressing all aspects of the project relating to:

Task 1: Development of the Physicochemical Properties Calculator

Task 2: Development of the Reaction Pathway Simulator

Additional work was also conducted outside of the scope of the SERDP Project. The focus of this work is related to the development of the Chemical Editor and the Structure-Based Database. These additional components, described below, are critical to the development of a fully deployable Chemical Transformation Simulator.

Background

Processes Controlling the Environmental Fate and Transport of Munition Compounds

The cumulative knowledge base resulting from laboratory and field-based studies of the N-based munitions and related chemicals indicate that dissolution (will not be addressed in this proposal), physical (i.e., reversible) sorption to soil organic matter, chemical (i.e., irreversible) sorption to soil organic matter through covalent binding, reductive transformation, and hydrolytic ring opening of heterocyclic nitramines are the primary physical and chemical processes controlling their reactive transport through soil, sediment and aquatic ecosystems. Predicting the extent and rates of these processes requires knowledge of both the chemical and environmental system of interest. For example, the extent of physical sorption can be accurately predicted with the octanol/water partition coefficient and the organic carbon content of the soil or sediment of interest. Although our understanding of the molecular and environmental properties controlling covalent binding and reductive transformation have progressed significantly in the past 5 years, computation tools that incorporate this growing knowledge base are not yet available. Such tools would allow for the application of this knowledge base to new and proposed munition compounds.

Physical Sorption

The physical sorption of the N-based munition compounds, relatively speaking, is fairly well understood. In general, the polynitro aromatics (e.g., TNT) tend to sorb to soil and sediment surfaces at a greater extent than heterocyclic nitramines (e.g., RDX). This is expected, based on the measured octanol/water partition coefficient. In general, sorption of the polynitro aromatics are best characterized by Freudlich and Langmuir isotherms, whereas the heterocyclic nitramines are best characterized by the Freudlich linear isotherm [1]. Key soil properties affecting sorption include soil particle size, organic carbon content, and clay type (i.e., monovalent cation clays versus multivalent cation clays).

Chemical Sorption

The aromatics amine resulting from the reductive transformation of the polynitro aromatic munitions are highly reactive in soil and sediments. Sorption studies conducted in this laboratory of TNT and its reduction products in pond sediments has provided further insight into the relationship between compound structure, redox conditions and sorption mechanisms [2]. The general trend that emerges is that reversible sorption decreases with increasing substitution of amino groups for nitro groups [TNT > aminodinitrotoluenes (ADNTs) > diaminonitrotoluenes (DANTs] and that irreversible sorption increases over this same series. Daun et. al. [3] report this same trend for the covalent binding of TNT, 4-ADNT, 2, 4-DANT and TAT with humic acids. TNT and the ADNTs sorbed through reversible mechanisms, showing complete or near-complete recovery of the compound. As expected, sorption of these compounds are unaffected by changes in redox conditions. On the other hand, sorption of the DANTs is dominated by an irreversible process that is dependent on redox conditions.

The increase in irreversible sorption with increasing substitution of amino groups for nitro groups (TNT>(ADNTs>DANTs) is consistent with our knowledge of covalent binding. Due to the lone pair of electrons on the amino N-atom, aromatic amines are weak bases and potential nucleophiles at pH values above their pK_a's. Numerous studies have concluded that aromatic

amines can undergo nucleophilic addition to carbonyl moieties in the organic matrix of the sediment [4-8]. The potential for covalent binding through nucleophilic addition is expected to increase with N-electron density. In the same context, the acidity of the amino group is indicative of its nucleophilic character [9]. TNT, having no amino substituents, cannot bind by nucleophilic addition. Because of the presence of two strong, electron-withdrawing nitro groups, 2-ADNT and 4-ADNT are only weak nucleophiles. Covalent binding though nucleophilic addition is improbable. 2,4-DANT and 2,6-DANT, however, have significant nucleophilic character and covalent binding is possible if electrophilic binding sites are present. It has also been proposed that the hydroxyl amine intermediates (Ar-NH-OH), formed along the reaction pathway for the reduction of TNT and DNT, can also covalently bind to natural organic matter (NOM) associated with soils and sediments.

A number of studies, including several conducted in this laboratory, have focused on elucidating the irreversible sorption of chemical contaminants with aromatic amine functional groups in soil and sediment sediments [4, 5, 10-14]. Irreversible binding of aromatic amines to carbonyl moieties in the natural organic matter (NOM) (e.g. via 1,4-nucleophilic addition to quinone moieties) is thought to be the predominant pathway governing their fate in the environment [4, 5, 7]. ^{15}N-NMR studies of the reaction of ^{15}N-aniline with model compounds and humic acids have demonstrated that quinone moieties are the dominant electrophilic site for covalent binding [8], which is consistent with the observation that aromatic amines have greater stability under strongly reducing conditions compared to oxic conditions. As redox conditions become more reducing it is hypothesized that there will be a shift of the quinone-hydroquinone equilibrium to the hydroquinone effectively blocking covalent binding through 1,4-nucleophilic addition to the quinone moiety. QSAR analysis of the reaction kinetics for the irreversible binding of monosubstiuted anilines to soil organic matter indicates that ionization constants, which are a measure of the aromatic amine's nucleophilicity, were the best molecular descriptors for predicting rates of covalent binding [15]. This observation provides further evidence that this reaction process is occurring primarily through nucleophilic addition to electrophilic moieties in the NOM.

Reductive Transformation

Numerous laboratory and field studies of the N-based munition chemicals and related chemicals (e.g., nitro aromatics and aromatic N-nitrosoamines) indicate that reductive transformation is the primary transformation process of these chemical in anoxic systems [16-21]. The incorporation of this reaction process into the proposed environmental fate simulator requires knowledge of the reductants in natural systems and the properties of the munition compounds that describe its "willingness" to accept electrons. Although our understanding of reductive transformations in the environment has progressed to the point that we can identify the functional groups that will be susceptible to reduction and the molecular descriptors that are needed to predict reactivity, identifying the pathways for electron transfer has been the greatest source of uncertainty for the prediction of reduction rates in natural systems. The obvious questions remain "What are the sources of electrons in naturally reducing environments?", and "How can these sources be quantified?"

The chemical reductants that have been proposed to contribute to the reductive transformation of nitroaromatic compounds (NACs) in anaerobic systems include ferrous iron adsorbed to iron-bearing mineral oxides [22-24], iron sulfides [25-28], dissolved sulfide species,

[29], and sulfide in the presence of quinones [30-32]. The occurrence of these chemical reductants anaerobic systems is a result of the reduction of inorganic electron acceptors coupled to the microbial oxidation of organic matter. Studies of model systems designed specifically to mimic iron- and sulfate-reducing conditions have provided much insight into the possible processes controlling the reductive transformation of NACs under these redox conditions [24, 33, 34]. The general conclusion drawn from these model studies is the importance of surface-associated,ferrous iron (Fe(II))as a chemical reductant for the reductive transformation of NACs. The role of surface associated Fe(II) has also been demonstrated in laboratory studies for both the polynitroaromatics and heterocyclic nitramines.

More recent studies in ERD have demonstrated that Fe(II) associated with amorphous iron minerals and reduced dissolved organic matter, a solution phase reductant, are the predominant reductants in more than 20 anaerobic sediments (non-sulfate containing) collected across the country [35]. In the sediments with organic carbon of < 5%, surface associated Fe(II) was the predominate reductant, accounting for ~75 % of the variation in measured reactivity. Furthermore, we determined that the use of soluble Fe(II) and %OC/DOC concentrations are readily measurable indicators of sediment reactivity. This determination will significantly simplify the estimation of the reaction rates in reducing environments. These findings have important implications concerning our ability to predict rates of reductive transformation in anoxic systems.

Hydrolytic ring opening of heterocyclic nitramines

A growing body of evidence in the literature has demonstrated the significance of the ring opening of heterocyclic nitramines as transformation process controlling their ultimate fate in soils, sediments and sludge [18, 19, 36, 37]. The significance of this reaction is that the key ring cleavage intermediate formed in this process (i.e., methylenedintramine) is susceptible to further biodegradation resulting in the formation of N_20 and CO_2. Developing the capability to predict reaction rates for this could be of significance in the design of future heterocyclic nitramines, where this degradation pathway is “maximized”; ensuring complete biodegradation of the munition compound into harmless products. Methylenedinitramine from RDX degradation can form from either direct enzymatic hydrolysis of the parent heterocyclic nitramine, and/or hydrolytic cleavage of mononitroso reduction intermediate, which, upon further reduction to the hydroxylamine intermediate; is then susceptible to ring opening, through hydrolysis [37].

Results and Discussion

Major Software Components of the CTS

The major components of the CTS developed to successfully reach the stated goals of this project include:

Chemical Editor (CE): allows the user to enter the chemical(s) of interest by providing a chemical structure, SMILES string, CAS# or common name.

Reaction Pathway Simulator (RPS): based on chemical structure analysis, provides the dominant transformation products as a function of environmental conditions (Development of the RPS is the focus of Task 2).

Physicochemical Properties Calculator (PPC): provides the necessary molecular descriptors through linkage to molecular calculators (Development of the PPC is the focus of Task 1).

The components of the CTS that are currently being developed outside the scope of the SERDP project include:

Structure Searchable Database (SBD): Database for the storage of the calculated and measured physicochemical properties required for estimating environmental concentrations.
The milestone associated with the development of the SBD, which is currently listed under the PPC, is listed below.

Environmental Systems Model (ESM): Provides the necessary environmental descriptors through linkage to web-accessible databases.

The current status for each of these major components is provided in the following discussion. It should be noted that EPA's Office of Research and Development has made a long-term commitment through its National Research Program for Chemical Safety and Sustainability to support the continued development and support of the CTS. Figure 1 provides the schedule for the release of the current α-1.0 version of the CTS, as well as the α-1.1, β-version and fully-deployable versions.

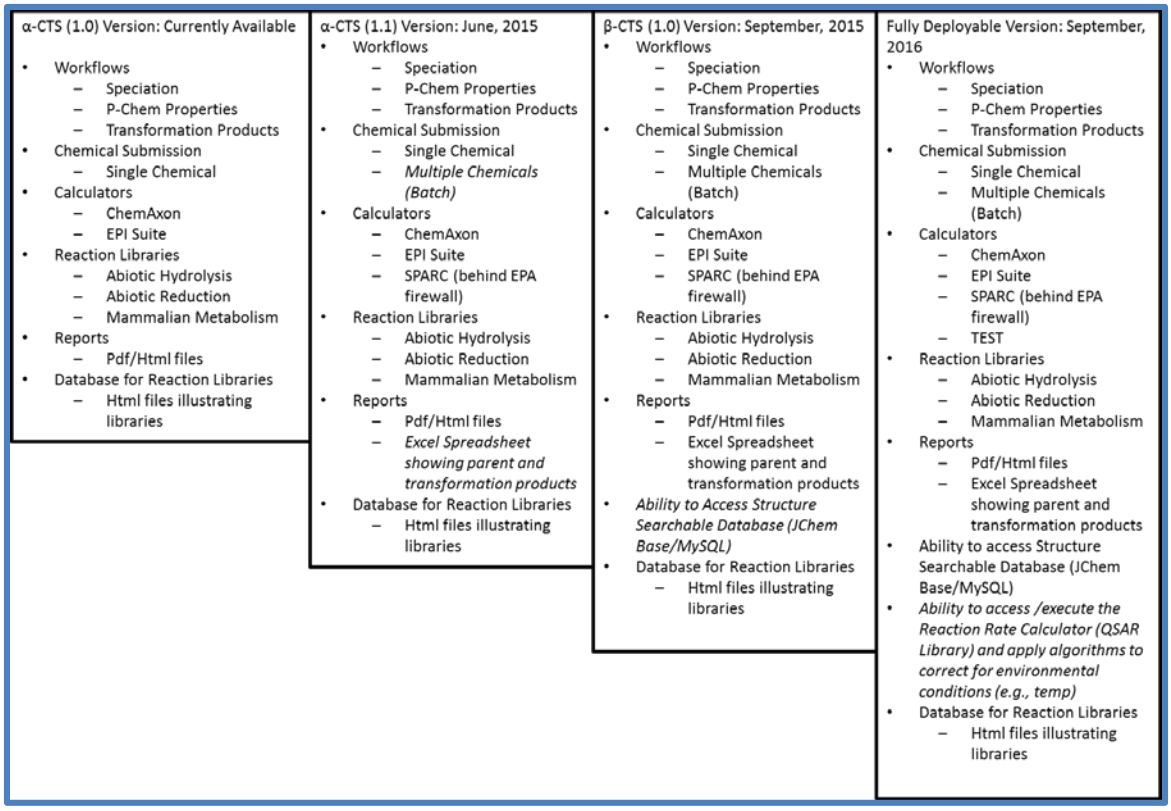


Figure 1. Schedule for the release of updated versions of the CTS. The new capabilities for each version are italicized.

As described in the SERDP proposal, our initial plan was to build the CTS based on SPARC's infrastructure. This decision was based on the knowledge that SPARC contains a chemical editor and has the ability to recognize functional groups based on SMILES string notation. Our inability to obtain the SPARC code, as well as the significant costs of reengineering SPARC to address our needs, dictated that we identify a different framework on which to build the CTS. The decision was made to move forward with the development of the CTS based in the integration of several cheminformatics applications developed by ChemAxon. These applications are serving as the basis for the chemical editor (MarvinSketch), the reaction pathway simulator (Metabolizer and Reactor) and the structure searchable database (JChembase).

The data flow diagram in Figure 2 illustrates how information will pass through the fully-functional CTS. The user input is the chemical of interest. The user will then has the option of executing the Reaction Pathway Simulator based on the environmental media of interest to generate potential transformation products, or execution of the Physicochemical Properties Calculator to generate molecular descriptors for the parent chemical. In future versions of the CTS, the output of the PPC will be stored in the structure-based database. The user will also have the option to generate reaction rate constants through the implementation of QSARs based on molecular descriptors (e.g., p*K*a values or one electron reduction potentials stored in the database) and environmental descriptors (e.g., pH and Fe(II) concentrations) as a function of geographical location through execution of the Earth System Model. The calculated first-order rate constants will then be entered seamlessly into the database.

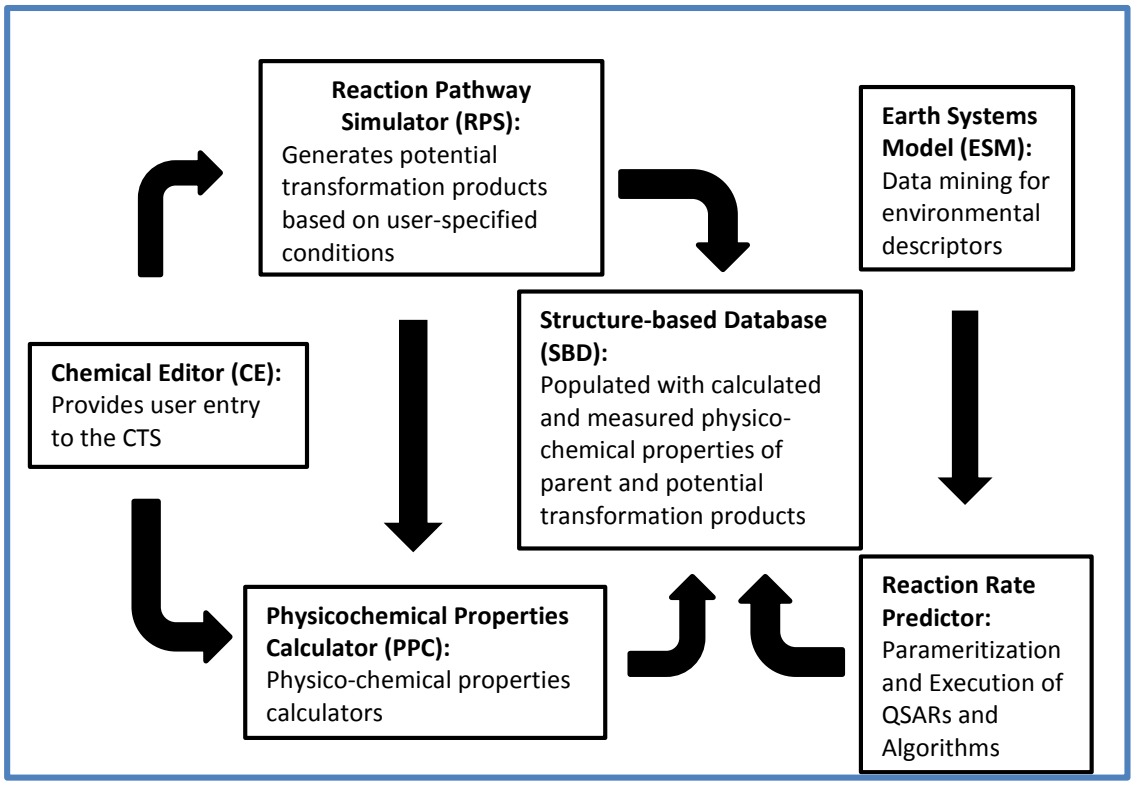


Figure 2. Data flow diagram for the Chemical Transformation Simulator.

Chemical Editor (CE): The CE allows the user to enter the chemical(s) of interest by providing a chemical structure, SMILES string, CAS# or common name. A screen shot of the CE for showing the entry of 2,4-DNAN by drawing its chemical structure is illustrated in Figure 3. The results of the chemical entry are illustrated in the lower box and the chemical drawing applet. For example, if the user enters the SMILES string for the chemical of interest, in addition to the SMILES string, the IUPAC name and CAS # will appear in the appropriate boxes. Also, the chemical structure will appear in chemical drawing applet.

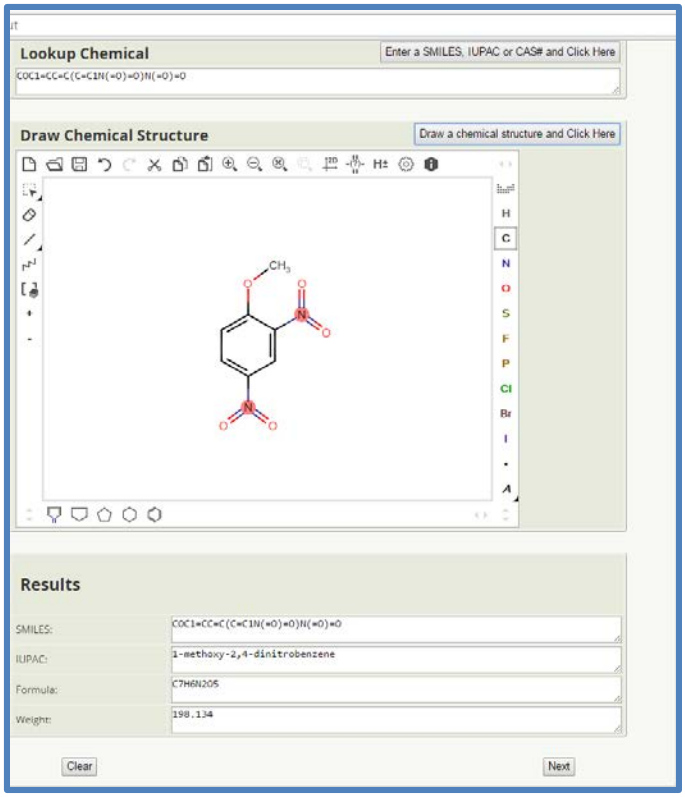


Figure 3. Screen shot of the Chemical Editor.

Reaction Pathway Simulator (RPS):

Development of the RPS is the focus of Task 2.0. The milestones under Task 2.0 include:

Milestone 2.1: Develop capability for identifying functional groups susceptible to reductive transformation and hydrolysis based on SMILES string notation

Milestone 2.2: Develop FRAMES-based capability for displaying reductive transformation products based on SMILES string notation

Although the RPS is functional upon selection of the chemical and the reaction conditions and transformation processes, the extension of the supporting reaction libraries (see discussion below) will continue throughout the life time of this project.

Construction of Reaction Libraries: The output of the RPS is based on the selection and execution of reaction libraries that represent one-step reactions for transformation of reactive functional groups (e.g., reduction and hydrolysis) as listed in Table 1. The actual reaction schemes, examples, and the data sources can be found in the Supporting Data Appendix. These one-step reactions represent viable transformation pathways based on the identification and subsequent transformation of reactive functional groups. The functional group transformations listed in Table 1 extend beyond those typically found in the N-based munitions. The expanded reaction libraries address other classes of chemicals (e.g., halogenated solvents) that are of interest to both DOD and

EPA. A reaction library for human metabolism for phase 1 transformations developed by ChemAxon is also available through the CTS.

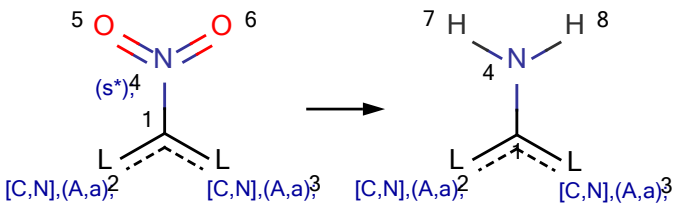
It is through the development of reaction libraries that is allowing us to "encode" the known process science published (current and future) published in the peer-reviewed literature, as well as the process science that is being generated through on-going SERDP research projects. The execution of these reaction libraries provides the dominant transformation pathways and products for the chemical of interest as a function of environmental conditions.

The encoding of the process science is accomplished through the use of Chemical Terms Language and Smart Reaction Smile string through the cheminformatics applications. Examples of NTO and nitrobenzene reduction (i.e., nitro group reduction), and as well as the reduction of 2,4DNAN (i.e., *Regioselective reduction of aromatic nitro groups*) in anaerobic systems are provided below.

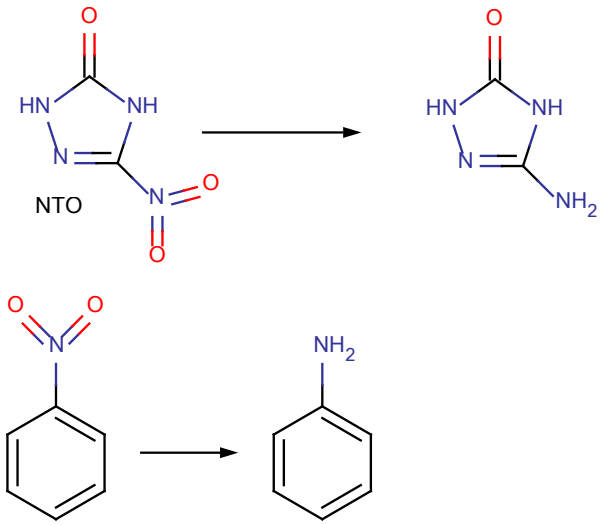
Abiotic Reduction Transformations	Hydrolysis Transformations
1. Hydrogenolysis	1. Halogenated aliphatics: Nucleophilic Substitution
2. Vicinal dehalogenation	2. Halogenated aliphatics: Elimination
3. Nitroaromatic reduction	3. Epoxide hydrolysis
4. Aromatic azo reduction	4. Organophosphorous ester hydrolysis: Pathway 1
5. Sulfoxide reduction	5. Organophosphorous ester hydrolysis: Pathway 2
6. N-Nitrosamine reduction	6. Carboxylic acid hydrolysis
7. Quinone reduction	7. Anhydride hydrolysis
8. Isoxazole Cleavage	8. Lactone Hydrolysis
9. Regioselective reduction of 1-substituted-2,4-dinitrobenzenes	9. Anhydride Hydrolysis
	10. Amide hydrolysis
	11. Lactam Hydrolysis
	12. Carbamate hydrolysis
	13. Urea hydrolysis
	14. Sulfonylurea Hydrolysis
	15. Thiocarbamate Hydrolysis
	16. Nitrile Hydrolysis
	17. N-S Bond Cleavage

Table 1. Reaction libraries for reduction and hydrolysis that represent one-step reactions for the transformation of reactive functional groups. The highlighted reactions correspond to the transformation of functional groups most often found in the N-based munitions.

Nitro group reduction. A large body of information exists in the peer-reviewed literature demonstrating that aromatic and aliphatic nitro groups are susceptible to reduction to amino groups in anaerobic and microbial systems[16, 38-45]. The Chemical Terms Language allows us to develop a generalized reaction scheme that captures this process science:



This reaction scheme indicates that the carbon atom bearing the nitro group can be bonded to either carbon (C) or nitrogen (N), and that these atoms can be aromatic (A) or aliphatic (a) in nature. As illustrated in the following scheme, the execution of this reaction scheme for NTO results the formation of 5-amino-l,2,4-triazol-3-one, which has been shown to occur in cytochrome P-450.[46]. Likewise the reduction of an aromatic nitrobenzene, such as nitrobenzene, results in the formation of aniline:



Regioselective reduction of aromatic nitro groups. Studies conducted previously in our lab demonstrated that reduction of 2,4-dinitrobenzenes with Br, Cl, OH, or OCH_3 substituents in the 1-position within an abiotic reducing model system were very selective (98 to 100%) for the nitro group in the 2 position[47]. This reaction sequence is illustrated for 2,4DNAN in Figure 4. Conversely, when a methyl group is in the 1-position, reduction of the nitro groups in the 4-position is preferred. Again, this process science can be captured through the use of Smart Reaction SMILES string generated in the cheminformatics applications.

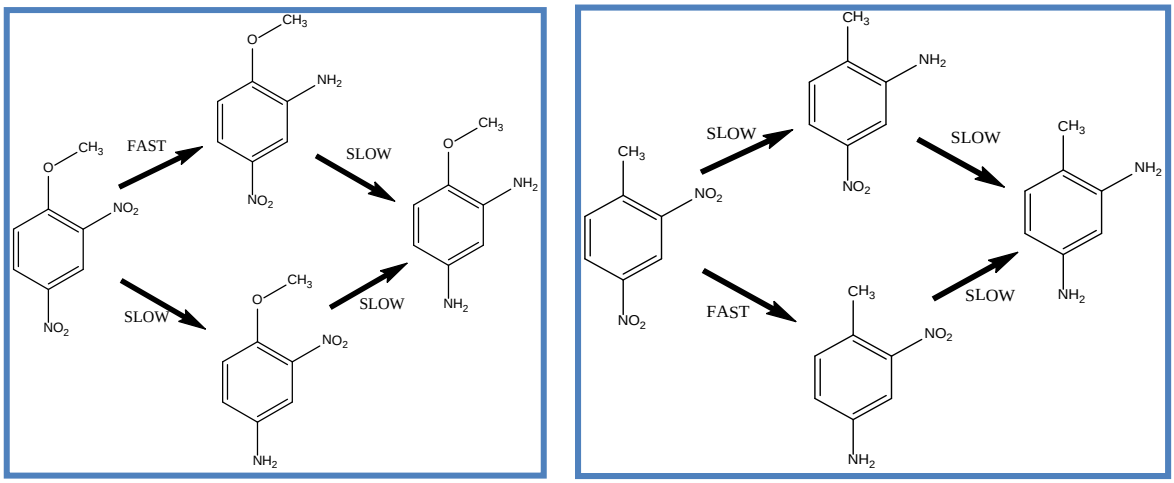
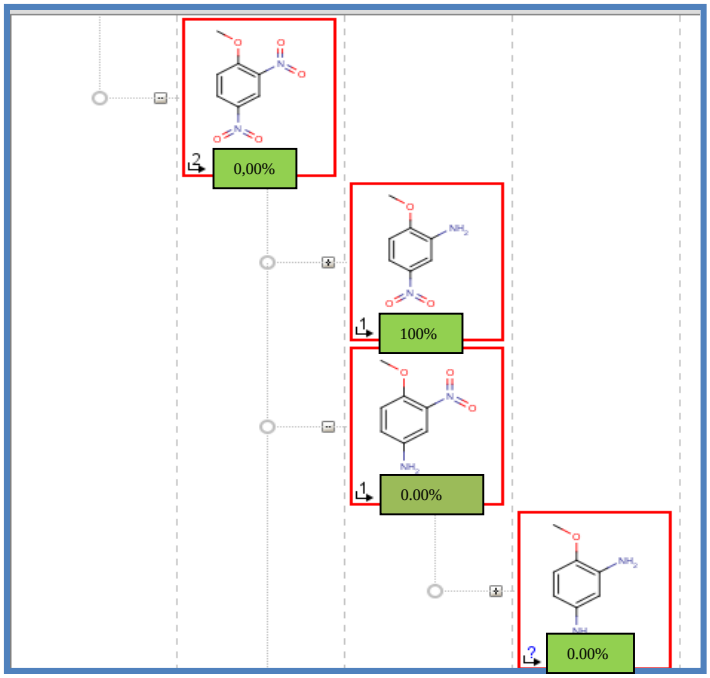


Figure 4. The reaction pathways for the reduction of 2,4DNAN and 2,4DNT in an abiotic reducing model system.

For example, the reduction of the 2,4-dinitrobenzene with either a halogen, hydroxy or methoxy group in the one postion to form the 1-substitued-2-amino-4-nitrobenzene is represented by the following smart reaction SMILES string:

[F,Cl,Br,I,O,OC:11][c:1]1[cH:2][cH:3][c:4]([cH:5][c:6]1[N:7](=[O:12])=[O:13])[N:8](=[O:9])=[O:10]>>[NH2:7][c:6]1[cH:5][c:4]([cH:3][cH:2][c:1]1[F,Cl,Br,I,O,OC:11])[N:8](=[O:9])=[O:10]

The basis for determining % accumulation of a given transformation product is based on the assignment of speed categories that will be available in the α-1.1 version of the CTS. Figure 5 illustrates the output that will be generated by the RPS for reduction of 2,4DNAN under anaerobic conditions once the speed categories have been assigned to the individual transformations in the reaction libraries. Based on the assigned speed categories for each of the individual transformation steps, 4A2NA is the dominant formed transformation product, based on the fact that its rate of formation is expected to be fast, and its rate of subsequent loss is expected to be slow. The speed categories will be adjusted as more kinetic data become available.



% Accumulation is based on the assignment of speed categories:

1 = very slow (months to years)
2 = slow (weeks to months)
3 = neutral (days to weeks
4 = fast (hrs to days)
5 = very fast (min to hrs)

Figure 5. Transformation pathways generated for the reduction of 2,4DNAN through the RPS. % Accumulation is based on the assignment of speed categories to DNAN each of the individual transformation steps.

In addition to encoding the one-step reaction for reductive transformation and hydrolysis, we will also encode secondary reactions that can dominate the environmental fate of the reduction products and intermediates of the N-based munitions in anaerobic ecosystems (i.e., covalent binding and dimer formation).

Covalent Binding. Covalent (i.e., irreversible) binding occurs primarily through the reaction of the aromatic amines formed from the reduction of nitroaromatics and azo compounds with electrophilic moieties found in natural organic matter (NOM). Kinetic studies conducted earlier in our laboratory and N^{15}-NMR (nuclear magnetic resonance) experiments with colleagues at the USGS demonstrated that the dominant pathway for covalent binding occurs through 1,4-nucleophilic addition of aromatic amines to quinone moieties in the (NOM) associated with soils and sediments [38, 48]. Additional studies by the USGS group have demonstrated this pathway for the covalent binding for the reduction intermediates of TNT and DNT [49, 50]. This reaction pathway for covalent binding is illustrated for the nucleophilic addition of 2,4-diaminoanisole (2,4DAAN), a product formed in the reduction of 2,4DNAN, to benzoquinone, a model compound used to represent the quinone moieties in NOM. This example also illustrates our efforts to explore how the physicochemical property calculators in the cheminformatics applications can be exploited to further refine reactions rules governing reactivity and selectivity. The kinetic studies had revealed that the nucleophilicity of substituted anilines could be correlated with p*K*a values (i.e., the greater the p*K*a value the faster the rate for covalent binding). Also, it was determined that the p*K*a values for the amino groups must be > 4.5 for these reactions to occur at appreciable rates. Based on these kinetic data and the p*K*a values calculated for the amino groups (shown in brackets below), we can predict that the binding of the reduction products 2,4DNAN will not occur

until both nitro groups have been reduced, and that the amino group in the 4-position will be more reactive than the amino group in the 2-position.

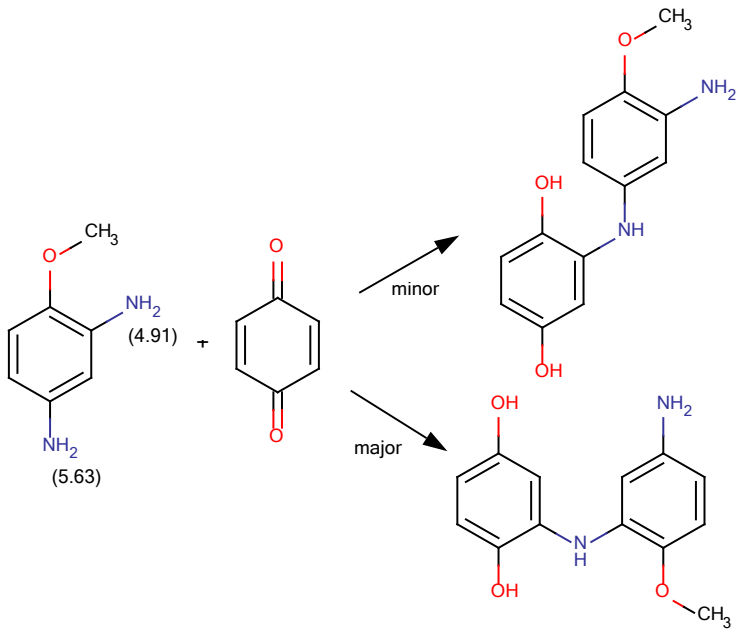


Figure 6. Reaction scheme for the nucleophilic addition of 2,4DAA to 1,4-benzoquinone.

Dimer Formation. Dimer formation occurs through reactions between intermediate reduction products to form dimers such as,azoxy and azo compounds. An example of dimer formation resulting from nucleophilic addition of DAAN to an N-nitrosamine reduction intermediate is illustrated below for the formation of an azo dimer. Azoxy dimer formation is also shown for the nucleophilic addition of an N-hydroxyl amine intermediate with the same N-nitroso intermediate. We have developed a reaction library for the possible dimerization reactions for the 2,4DNAN reduction intermediates that will be implemented in the β-version of the CTS. Due to the number of potential intermediates that can form from the reduction of 2,4DNAN, the formation of 8 unique dimers is possible. Work is now in progress to determine which pathways are expected to dominate under reducing conditions based on the use of the p*K*a and partial charge calculators. We anticipate that the experimental results that are being generated through several of the new SERDP Environmental Restoration projects (i.e., Projects ER-2220, ER-2221, and ER-2222) will provide us the ability to compare predicted pathways with experimentally determined pathways for dimer formation.

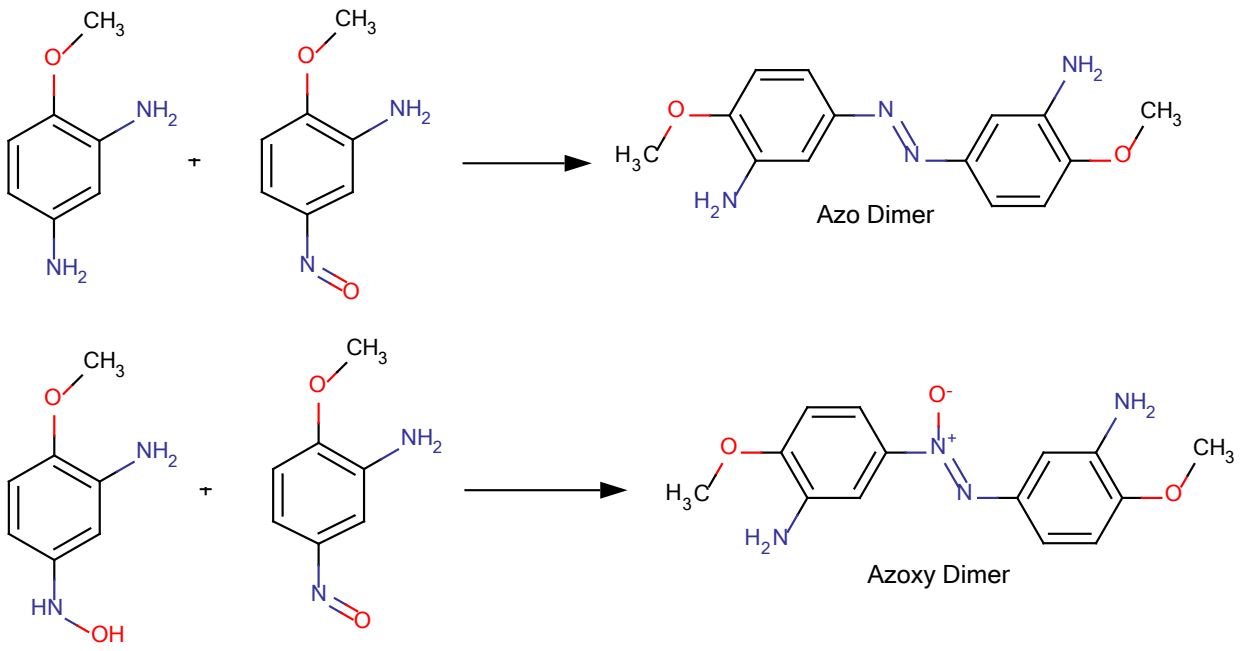


Figure 7. Reaction scheme for the formation of azo and azoxy dimers resulting from reactions of 2,4DNAN intermediate reduction products.

Physicochemical Properties Calculator (PPC):

The milestones associated with the development of the PPC are listed below.

Milestones:

1.1. Construct and populate database for all relevant environmental fate data for the N-based explosives (e.g., TNT, DNT, RDX, and HMX) and their known transformation products.
1.2. Implement algorithms in the environmental fate simulator to predict rate constants for reductive transformation of N-based explosives.
1.3. Implement algorithms to predict sediment binding of N-based explosives due to hydrophobic partitioning onto sediment organic carbon.
1.4. Implement algorithms to adjust reductive transformation rate constants for the effects of sediment binding.
1.5. Enhance SPARC calculators for calculating additional molecular descriptors for use in predicting the sediment binding and non-reductive transformations of military munitions.
1.6. Refine algorithms for the prediction of reductive transformation rate constants and sediment binding coefficients.
1.7. Interface environmental fate simulator with SPARC for the calculation of physicochemical properties and descriptors for reductive transformation reactions of N-based explosives.

Although the initial design was for linkage to only the SPARC calculator (Milestone 1.7), we have since expanded the design to providing a consensus approach to the calculation of p-chem

properties through the eventual linkage to 4 calculators that are based on different computational approaches:

- EPI Suite (Estimation Program Interface Suite): A fragment-based calculator
- Chemaxon Plug-in Calculator: Blend of mechanistic and QSAR-based approaches
- TEST (Toxicity Estimation Software Tool: QSAR-based approach using structural, topological and electrostatic descriptors
- SPARC (SPARC Performs Automated Reasoning in Chemistry): A mechanistic-based calculator

Access to the SPARC calculator will be available with the release of the β-version of the CTS and access to the TEST calculator will be available through the release of the fully deployable version of the CTS. This consensus approach to the calculation of p-chem properties will provide the user some idea of the error associated with the calculated data. Furthermore, the combination of these calculators provides full coverage of the necessary molecular descriptors for the parameterization of fate models and QSARs for estimating fate and transport in aquatic ecosystems. Table 3 provides a summary the physicochemical properties provided by each of the calculators. Any measured data that is found in the database associated with EPI Suite will also be provided to the user.

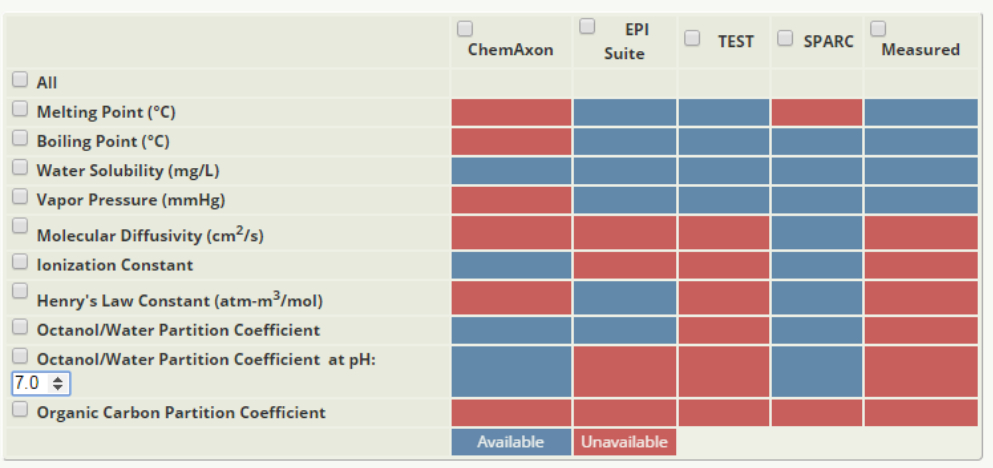


Table 2. The physicochemical properties that are provided by each of the computational tools in the PPC.

Milestone:

1.1. Construct and populate database for all relevant environmental fate data for the N-based explosives (e.g., TNT, DNT, RDX, and HMX) and their known transformation products.

Currently this database is a Lotus Excel file that was originally populated with a 1) list of emerging munitions and a list of constituents of concern that included existing munitions and other chemicals that were of concern to range managers. This list consisted of 207 chemicals. After this list of chemicals was submitted to the RPS to generate potential transformation products resulting from abiotic reduction and hydrolysis, this list was expanded to 702 chemicals. A subset of the spreadsheet is shown as an example in Figure 10. Also, included in the dataset are the p-chem properties calculated from the four p-chem calculators (data not shown).

SMILES String	Chemical Name	Transformation Process	Generation
[O-][N+](=O)C(Cl)(Cl)Cl	chloropicrin	50	0
[O-][N+](=O)C(Cl)Cl	dichloro(nitro)methane	Hydrogenolysis(50):1	1
[O-][N+](=O)CCl	methane, chloronitro-	Hydrogenolysis (50):1):1	2
Cc1cc(ccc1[N+]([O-])=O)C(=O)Nc1cc(cc(c1)C(O)=O)C(O)=O	5-(3-methyl-4-nitrobenzamido)benzene-1,3-dicarboxylic acid	51	0
CC1=CC(=CC=C1N)C(=O)NC1=CC(=CC(=C1)C(O)=O)C(O)=O	5-(4-amino-3-methylbenzamido)benzene-1,3-dicarboxylic acid	Nitroaromatic Reduction(51):1	1
Nc1cc(cc(c1O)[N+]([O-])=O)[N+]([O-])=O	**picramic acid**	**52**	**0**
NC1=CC(=CC(N)=C1O)[N+]([O-])=O	**2,6-diamino-4-nitrophenol**	**Nitroaromatic Reduction(52):1**	**1**
NC1=CC(=C(O)C(N)=C1)[N+]([O-])=O	**2,4-diamino-6-nitrophenol**	**Nitroaromatic Reduction(52):2**	**1**
NC1=CC(N)=C(O)C(N)=C1	**2,4,6-triaminophenol**	**Nitroaromatic Reduction (52):1):1**	**2**
NC1=CC(N)=C(O)C(N)=C1	**2,4,6-triaminophenol**	**Nitroaromatic Reduction (52):2):1**	**2**
NC(=N)N[N+]([O-])=O	nitroguanidine	53	0
[O-][N+](=O)N1CN(CN(C1)N=O)N=O	1-nitro-3,5-dinitroso-1,3,5-triazinane	54	0
O=NN1CNCN(C1)N=O	1,3-dinitroso-1,3,5-triazinane	N-Nitrosoamine Reduction(54):1	1
[O-][N+](=O)N1CNCN(C1)N=O	1-nitro-3-nitroso-1,3,5-triazinane	N-Nitrosoamine Reduction(54):2	1
O=NN1CNCNC1	1-nitroso-1,3,5-triazinane	N-Nitrosoamine Reduction (54):1):1	2
O=NN1CNCNC1	1-nitroso-1,3,5-triazinane	N-Nitrosoamine Reduction (54):2):1	2
[O-][N+](=O)N1CNCNC1	1-nitro-1,3,5-triazinane	N-Nitrosoamine Reduction (54):2):2	2
O=NN1CN(CN(C1)N=O)N=O	hexahydro-1,3,5-s-triazine	55	0
O=NN1CNCN(C1)N=O	1,3-dinitroso-1,3,5-triazinane	N-Nitrosoamine Reduction(55):1	1
O=NN1CNCNC1	1-nitroso-1,3,5-triazinane	N-Nitrosoamine Reduction (55):1):1	2

Table 3. A subset of the Excel database for the 702 chemicals of concern that includes the parent chemical and potential transformation products resulting from abiotic reduction and hydrolysis.

This database shows the relation between the parent chemical and transformation products, as well as the transformation process and the generation for each product was formed. For example, Figure 8 illustrates the transformation pathway for picramic acid through nitroaromatic reduction formed through two generations (highlighted in bold text).

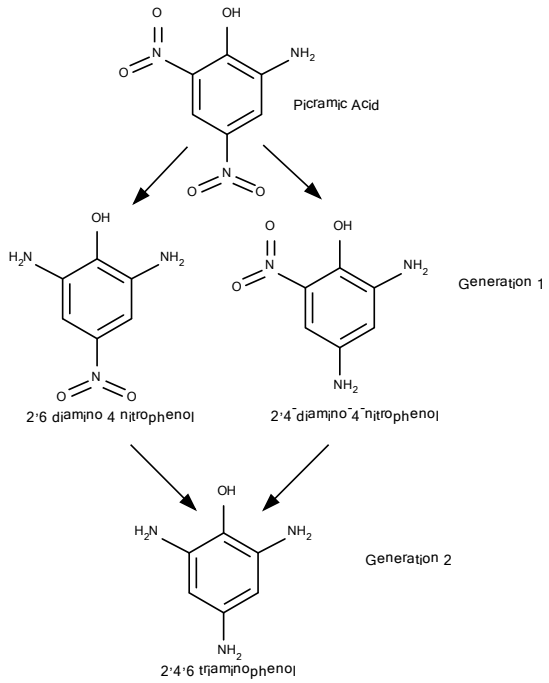


Figure 8. Transformation pathway for the reduction of picramic acid showing 1st and 2nd generation transformation products.

Implementation of algorithms. The collection and implementation of algorithms is addressed in Milestones 1.2, 1.3, 1.4, and 1.6.

1.2 Implement algorithms in the environmental fate simulator to predict rate constants for reductive transformation of N-based explosives.
1.3 Implement algorithms to predict sediment binding of N-based explosives due to hydrophobic partitioning onto sediment organic carbon.
1.4 Implement algorithms to adjust reductive transformation rate constants for the effects of sediment binding.
1.6 Refine algorithms for the prediction of reductive transformation rate constants and sediment binding coefficients.

Although not specifically stated, we also consider the implementation of QSARs a part of these milestones. The available algorithms and QSARs for predicting and adjusting rate constants for reduction and covalent binding are summarized in Figures 9 and 10. Although the algorithms and QSARs are currently being collected, they will not be fully implemented until the release of the fully deployable CTS.

Temperature:

$$k = Ae^{-\frac{E_a}{RT}}$$

where ***A*** is the frequency factor or pre-exponential factor and E_a is the activation energy (Default value for E_a = 50 kJ/mol)

Sorption:

$$k_{app} = \frac{k}{\left(1+\rho K_d\right)}$$

where k is the first-order rate constant for transformation in the aqueous phase, (K_d) is the sorption coefficient and ρ is the solid-to-solution ratio

Ionization :

where pK_a is the negative of the logarithm of the acid dissociation constant for the chemical

$$K_{d,app} = \left(\frac{1}{1+10^{pH-pK_a}}\right)K_{d,HA} + \left(\frac{10^{pH-pK_a}}{1+10^{pH-pK_a}}\right)K_{d,A^-}$$

Figure 9. Algorithms for adjusting reaction rate constants based on temperature, sorption and ionization.

Reduction:

–Fe(II)$_{ads}$/goethite:

Where E_1 is the one electron reduction potential

$\log k = (-0.53(\pm 0.04) \cdot E_1/0.059) + 4.0(\pm 0.3)$

k_{anaer} = - 0.0017 + 0.00017 **[aqueous Fe(II)]**

Where aq. Fe(II) is the aqueous Fe(II) concentration measured in anaerobic aquatic ecosystems

Covalent binding:

–Quinone addition:

Where pKa is the ionization constant

$\log k = (-0.411(\pm 0.04) \cdot \mathbf{pKa}) - 3.14(\pm 0.13)$

Figure 10. QSARs for the estimation of rate constants for reduction in anaerobic aquatic systems and covalent binding in soil and sediment systems

Structure Searchable Database (SBD): The SBD will serve the purpose of the storing calculated and measured physicochemical properties for the parent chemical and predicted transformation products. With the release of the fully-deployable version of the CTS, the database capabilities will be enhanced to include the ability to search on structure or substructure. An example of this database is provided in Table 4 for 2,4DNAN and its potential reduction products. Computed values are shown for log *K*ow and p*K*a for each of the calculators where applicable.

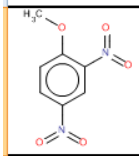
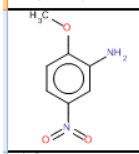
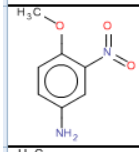
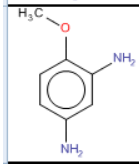
Structure	Compound Name	Smiles String	CAS #	Octanol Water Partition Coefficient (Kow) LOG				Ionization Constant (pKa) unitless					
				SPARC	EPI Suite	ChemAxon	Measured	SPARC		Epi Suite	ChemAxon		Measred
	Benzene, 1-methoxy-2,4-dinitro-	c1(OC)c(N(=O)=O)cc(N(=O)=O)cc1	119277	2.21	1.71	1.70							
	Benzenamine, 2-methoxy-5-nitro-	c1(OC)c(N)cc(N(=O)(=O))cc1	99592	1.03	1.47	0.93		1.98			2.15		
	p-Anisidine, 3-nitro-,	c1(OC)c(N(=O)(=O))cc(N)cc1	577720	2.04	1.55	0.93		2.98			3.03		
	1,3-Benzenediamine, 4-methoxy-	c1(OC)c(N)cc(N)cc1	615054	-0.81	-0.31	0.16		1.9	5.2		2.98	5.7	

Table 4. An example spreadsheet for 2,4DNAN and its potential reduction products. Computed values are shown for log *K*ow and p*K*a for each of the calculators, where applicable.

Environmental Systems Model (ESM): The ESM will provide the necessary environmental descriptors through linkage to web-accessible databases, as well as the parameritization of QSARS for the estimation of rate constants. Linkage to the USGS National Water Quality Database through D4EM (Data for Environmental Modeling will provide access to environmental descriptors such as temperature, pH, soil organic carbon and solution phase concentrations of ferrous iron in a site-specific manner. Figure 11 provides the output the ESM for the environmental descriptors of ESM based on the entry of a specific longitude and longitude. The ESM will be completely functional in the fully deployable version of the CTS.

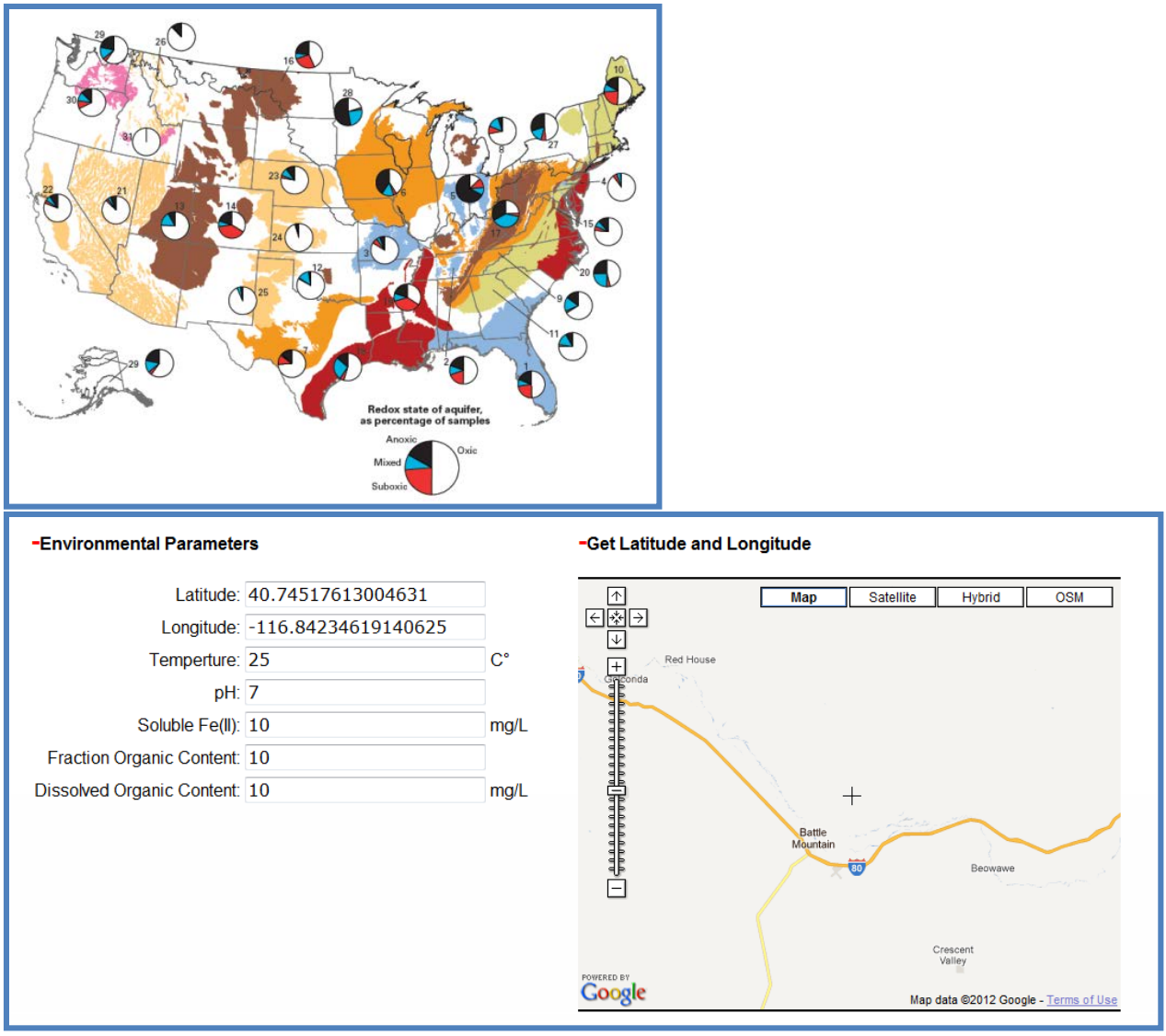


Figure 11. An example of environmental descriptors that will be accessible through D4EM from the USGS Water Quality database at a specific site based on a specified latitude/longitude

Running the CTS Software

This section is meant to give the reader a general overview of the software structure supporting the CTS, and how the major components are linked to one another. The detailed step-by-step process for running the CTS is provided in the Users Guide (see Appendix C). The CTS is running on five servers in the EPA approved ERD/CGI Federal Cloud. The CTS can be accessed at http://134.67.114.1/cts/. Figure 12 provides a screen shot of the CTS homepage.

Figure 12. Screen shot of the CTS homepage.

The user executes the CTS through the selection of one of three available workflows:

- Calculate Chemical Speciation
- Calculate p-Chem Properties
- Generate Transformation Products

For each of the three workflows, the user is taken to the Chemical Editor, whereas described earlier, they have the option to either enter a SMILES String, IUPAC chemical name, or CAS# in the Lookup Chemical box, or to draw a chemical structure using the Chemical Editor.

Selection of the Calculate Chemical Speciation Workflow

Selection of the Calculate Chemical Speciation workflow provides the user with the overview for this workflow, which illustrates the three options for calculating chemical speciation (Figure 13):

- Calculate Ionization Constants
- Calculate Dominant Tautomer Distribution
- Calculate Stereoisomers

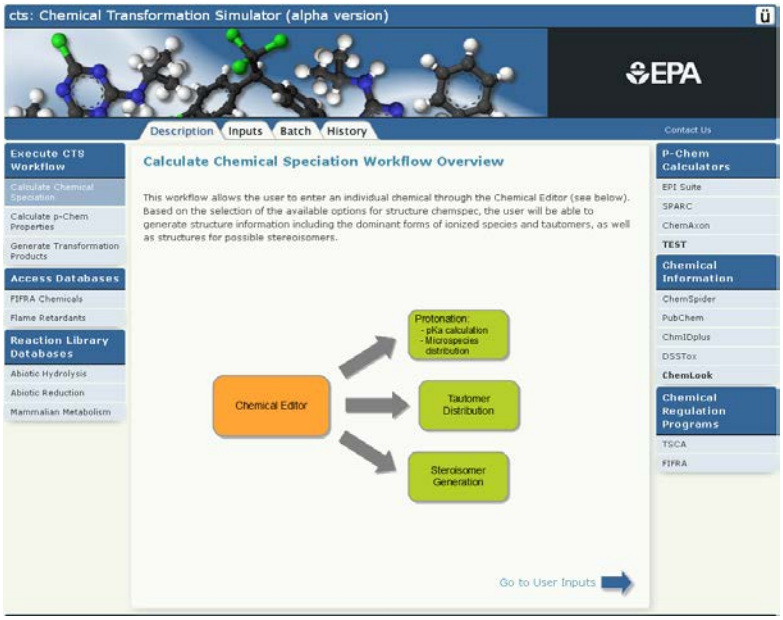


Figure 13: Overview of the Calculate Chemical Speciation Workflow.

The user can select any combination of the calculators. The user has the option to use the provided default values or to change the default values to values required by the user. As an example of the output for this workflow, the results for the ionization constant calculation are illustrated in Figure 14 for 4-aminophenol. This output includes:

- User Inputs: The molecular information and ionization parameters provided by the user
- pKa calculations: Provides the user with chemical structure entered by the user, the generated microspecies, and the distribution of microspecies as a function of pH over the pH range specified by the user. These results are color coded.
- Isoelectric point: The isoelectric point is provided as well as a graph illustrating the charge on the chemical as a function of pH.
- Major Microspecies:
  The dominant microspecies formed at the pH selected by the user.

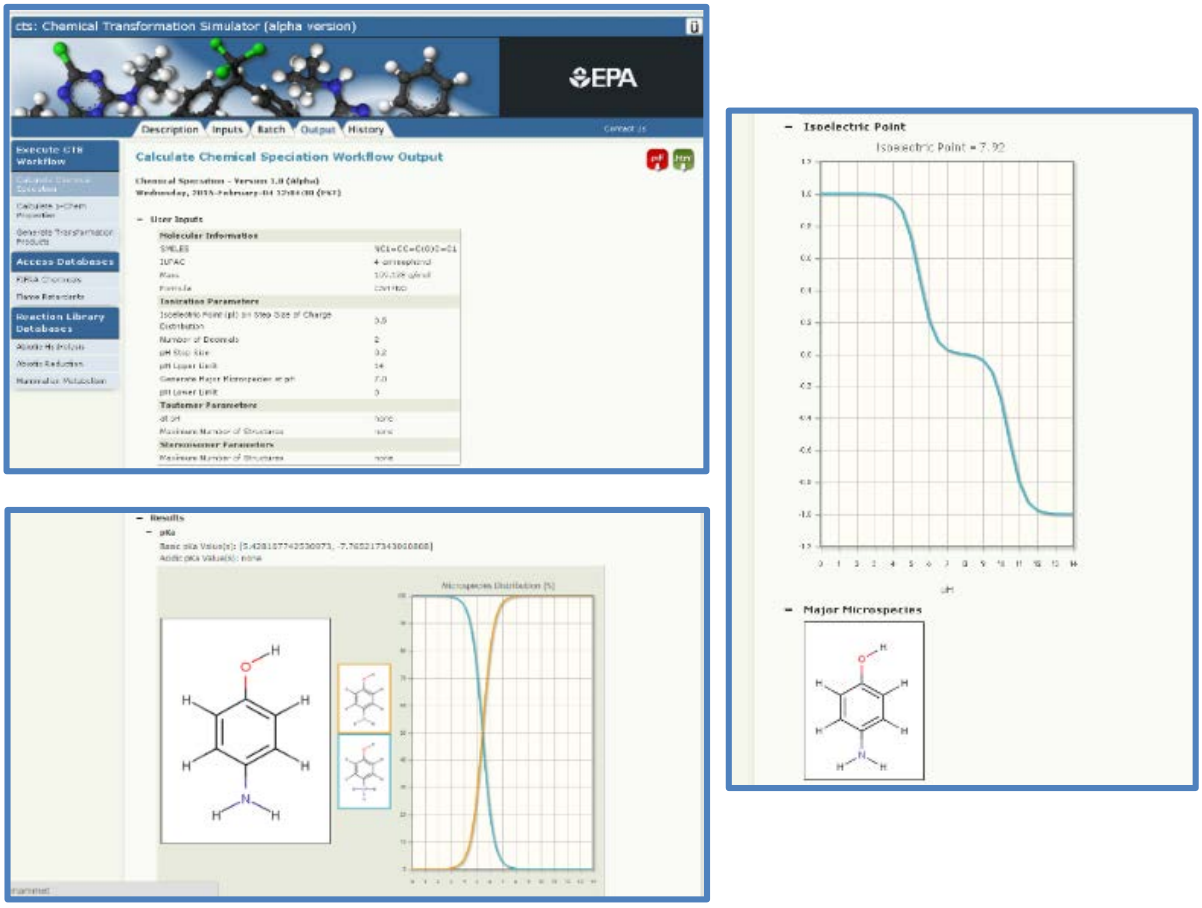


Figure 14. Results for the ionization constant calculation for 4-aminophenol.

Selection of the Calculate p-Chem Properties Workflow

Selection of the Calculate p-Chem Properties Workflow provides a page illustrating the workflow overview (Figure 15).

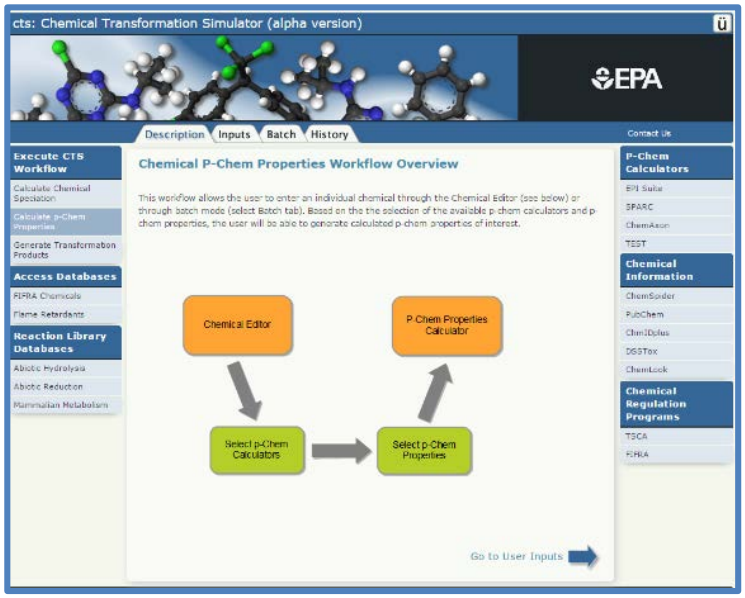


Figure 15: Overview of the Calculate p-Chem Properties Workflow.

The Chemical p-Chem Properties Workflow Inputs screen provides the user with the options to select p-chem properties and the p-chem calculators of interest (Figure 16). Selection of the All button for the p-chem properties will provide only the available properties for the selected p-chem calculators.

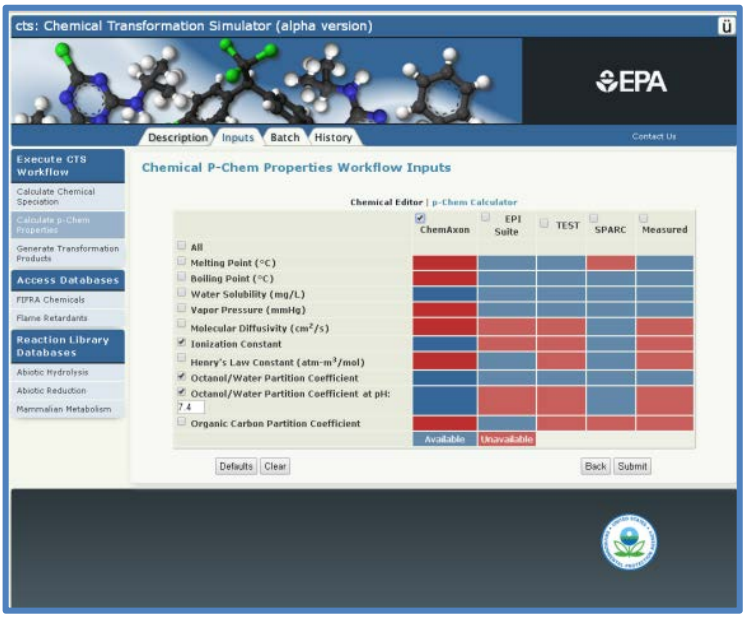


Figure 16. Input screen for the Chemical p-Chem Properties Workflow.

The Chemical p-Chem Properties Workflow Outputs screen provides the user with the results of the previously selected p-chem properties (Figure 17).

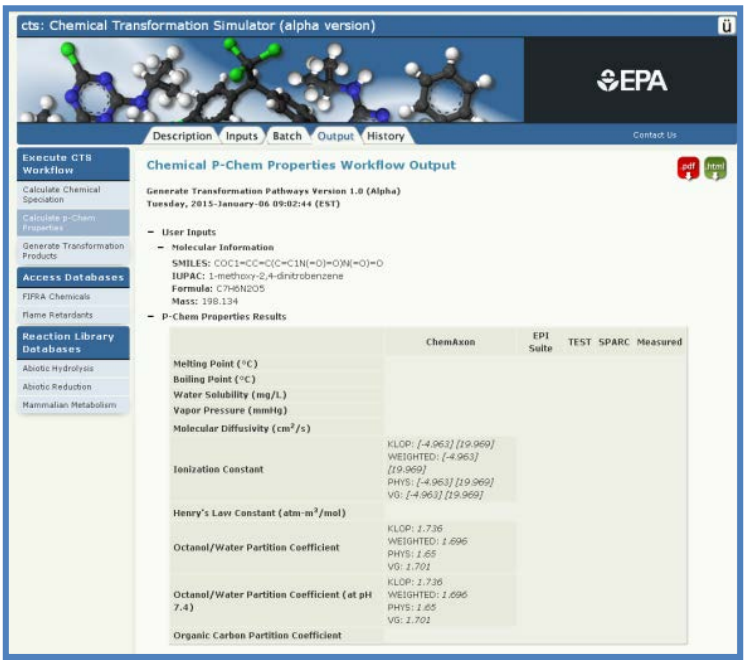


Figure 17. Output screen for the Chemical p-Chem Properties Workflow.

Selection of Generate Transformation Products Workflow

Selection of the Generate Transformation Products Workflow provides an overview of the workflow (Figure 18).

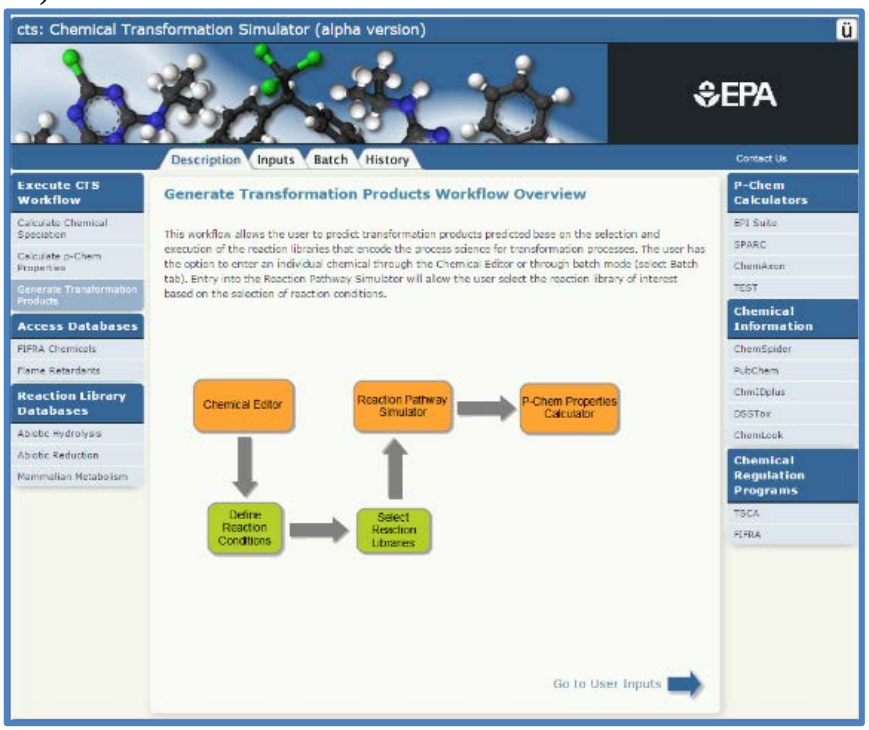


Figure 18. Overview of the Generate Transformation Products Workflow.

Prior to execution of RPS the user must select the reaction libraries of interest based on three options:

(1) the reaction medium of interest,
(2) the OECD test guideline(s) of interest
(3) the direct selection of the reaction libraries.

Options 1 and 2 will determine which of the reaction libraries will be executed in the RPS. Options will be limited based on the user's selection. For example, if the user selects anaerobic respiration conditions, benthic sediment or vadose zone/groundwater will be the only available options to the user (Figure 19). Following this example, the transformation processes would be limited to abiotic reduction, abiotic hydrolysis, or anaerobic biodegradation. Furthermore, only those transformation processes that are currently supported by reaction libraries will be functional, which include abiotic reduction and hydrolysis.

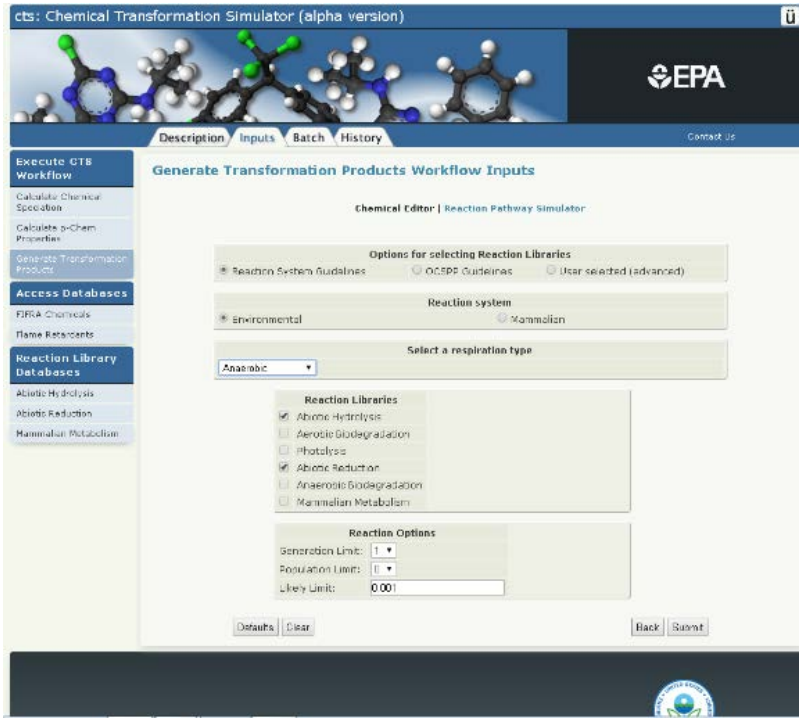


Figure 19. The first option for selection of transformation processes based on the selected respiration conditions and reaction media

After selection of the reaction libraries and reaction options have been made, the user clicks the submit key to generate transformation products. The results screen summarizes the input data and provides the 1st generation of transformation products (the default value) based on execution of the abiotic hydrolysis and reduction libraries. The user can expand the number of viewed generations using the drop down at the top left hand corner of the reaction pathway map.

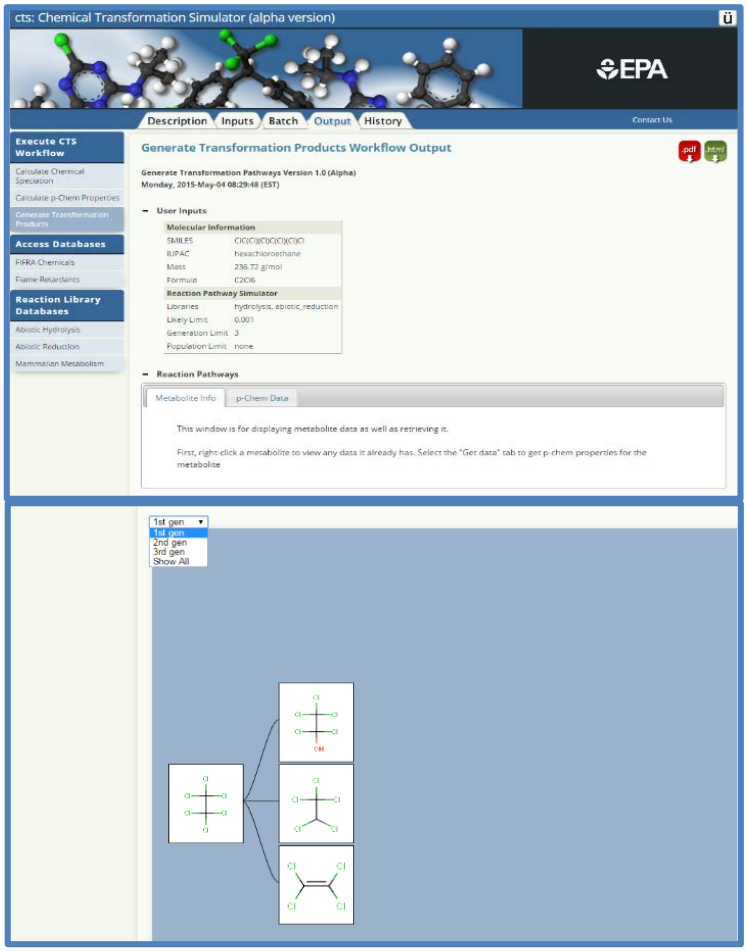


Figure 20: Example of the Generate Transformation Products Output screen

Selection of the p-Chem Data tab under Reaction Pathways provides the screen on the left below with the various options for p-chem properties and calculators to be applied to the selected transformation product. P-chem properties will be calculated and displayed in the selection table. For example, selection of the All and ChemAxon buttons and then the get data button provides the screen on the right below showing the results for the ChemAxon p-chem calculator for pentachloroethanol.

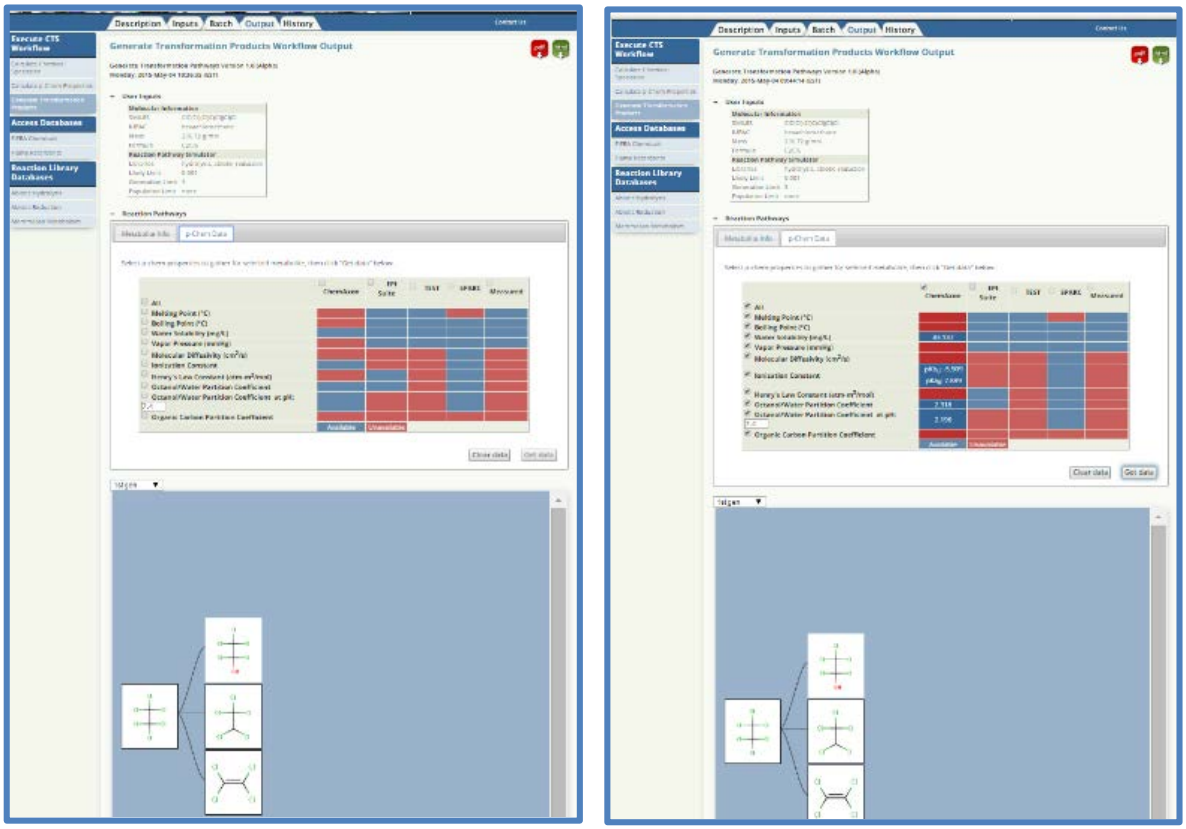


Figure 21: Example of the results output screen for the calculation of p-chem properties of transformation products formed in the Generate Transformation Products Workflow.

Conclusions and Implications for Future Research/Implementation

The greatest challenge we faced at the beginning of this project was the developing the technology for the encoding of the available process science concerning the environmental fate and transport N-based munitions. The decision to move away from the SPARC architecture for this purpose coupled with the discovery and implementation of existing cheminformatics applications has been crucial to the overall success of this project. The development of the major components of the CTS based on the cheminformatics applications, as well as the integration of the software technologies such as D4EM, have provided the required capabilities for each of these components. The use of Chemical Terms Language and the associated plug-in calculators are providing us the ability to encode the existing process science in the peer-reviewed literature, as well as the process science that is being generated from on-going SERDP projects. We are just beginning to explore the full potential of the plug-in calculators for the development of reaction rules governing reactivity and selectivity in support of the one-step reactions for the transformation of reactive

functional groups. Our sense moving forward is that we are no longer controlled by the availability of technology, but by the lack of the process science supporting the environmental fate on the new munition compounds.

A key challenge for us this coming year is to develop an automated process for the parameritization of QSARs for the estimation of first-order rate constants, which can then be used for calculating the % formation of the transformation products in the RPS. This will allow us to move from the qualitative approach of assigning speed categories to individual reactions to a more quantitative approach based on the estimation of first order rate constants.

Discussions over the past several months with the developers of TREECS (Training Range Environmental Evaluation and Characterization System) have been invaluable to the design and development of the PPC and the SBD. These discussions have provided us with the specific physicochemical properties that are required for the parameritization of the environmental fate and transport models currently in use for conducting exposure assessments at live fire training and test ranges.

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Appendices

Supporting Data

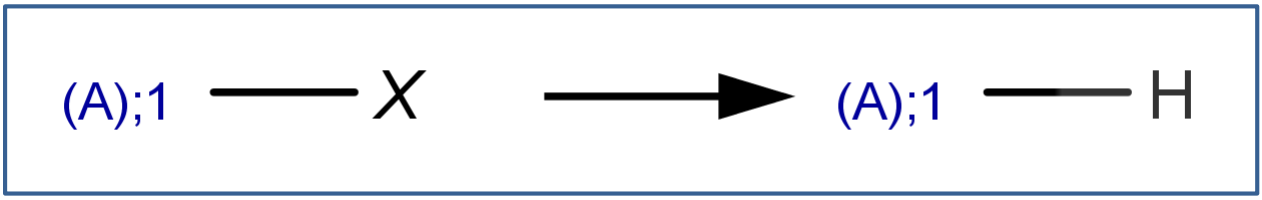
Abiotic Reduction Library

Version 1.4 of the Abiotic Reduction Reaction Library contains eight reaction schemes:

- Hydrogenolysis
- Vicinal Dehalogenation
- Nitroaromatic Reduction
- Aromatic Azo Reduction
- Sulfoxide Reduction
- N-Nitrosamine Reduction
- Quinone Reduction
- Isoxazole Cleavage

Hydrogenolysis

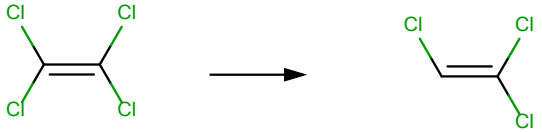
SCHEME:



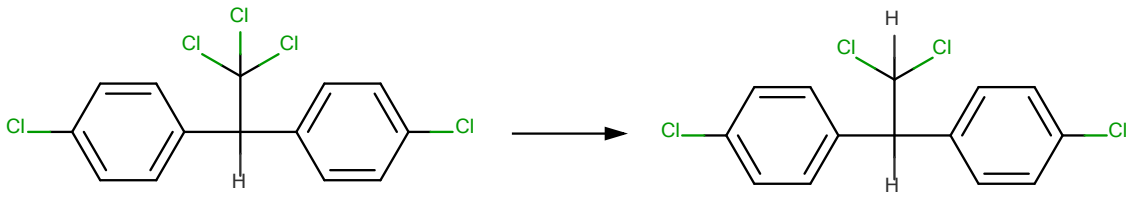
EXAMPLES:

- Carbon tetrachloride (Elsner et al., 2004)

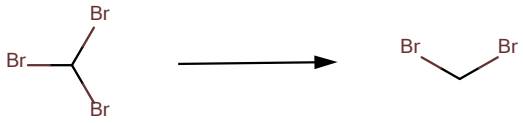
- Tetrachloroethene (Butler and Hayes, 1999)



- Dichlorodiphenyltrichloroethane (DDT) (Macalady et al., 1986; Larson and Weber, 1994)



- Tribromomethane (Perlinger et al., 1998)



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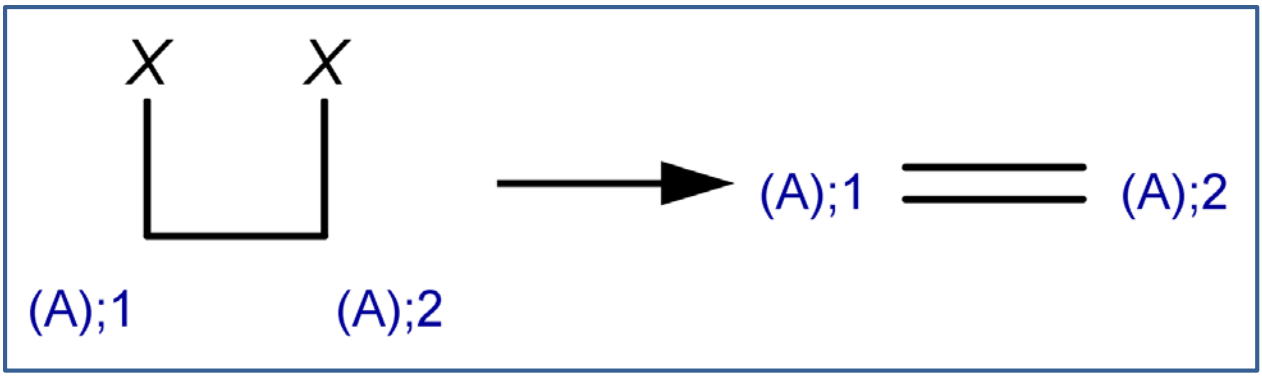
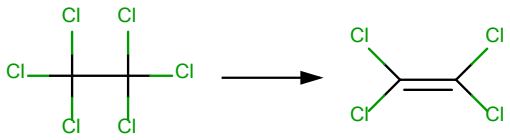
Vicinal Dehalogenation

SCHEME:



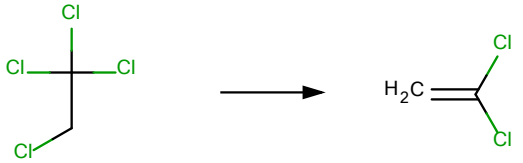
EXAMPLES:

- Hexachloroethane (Perlinger et al., 1996)



- 1,1,1,2-tetrachloro-2,2-bis(p-chlorophenyl)ethane (Alpha-chloro-DDT, DTE) (Macalady et al., 1986; Larson and Weber, 1994)

- Tetrachloroethane (Butler and Hayes, 2000)



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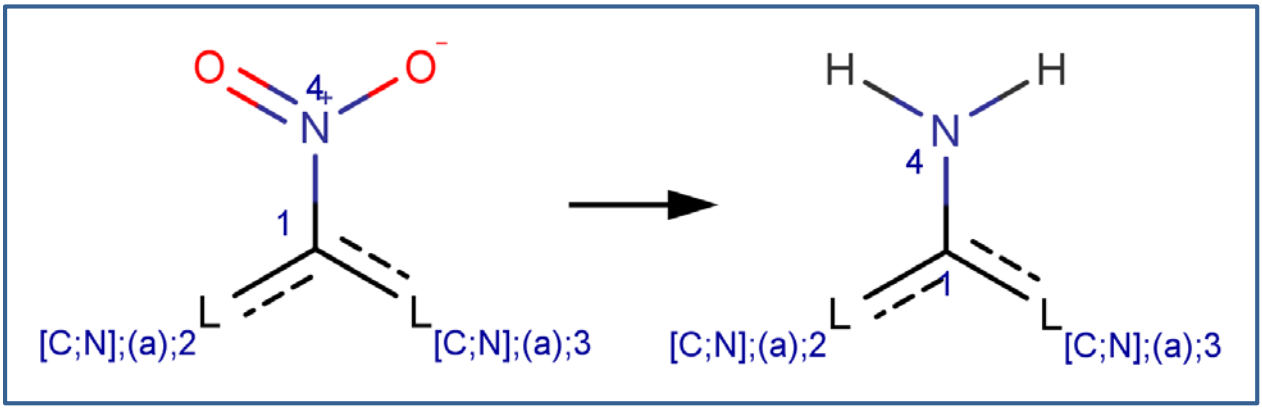
Larson, R.A. and E.J. Weber. *Reaction Mechanisms in Environmental Organic Chemistry*. Boca Raton: CRC Press, Inc., 1994.

Butler, E.C.; Hayes, K.F. Kinetics of the Transformation of Halogenated Aliphatic Compounds by Iron Sulfide. *Environ. Sci. Technol.* **2000**, *34*, 422-429.

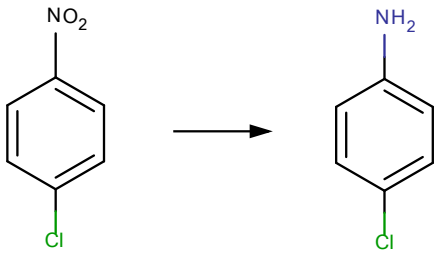
Nitroaromatic Reduction

SCHEME:

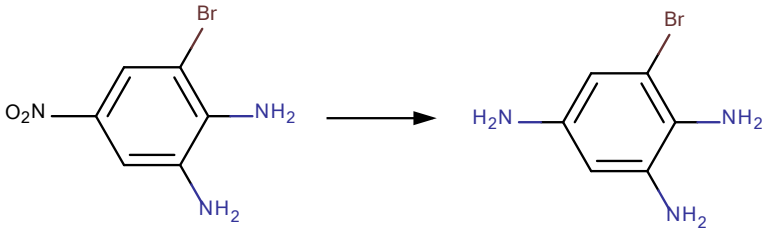


EXAMPLES:

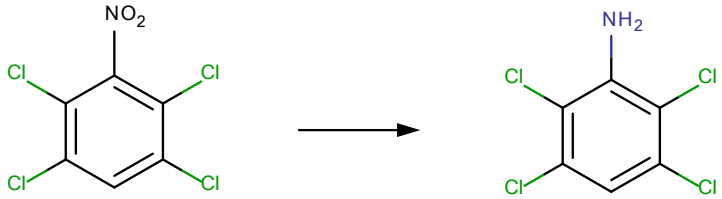
- P-Chloronitrobenzene (Klausen et al., 1995)



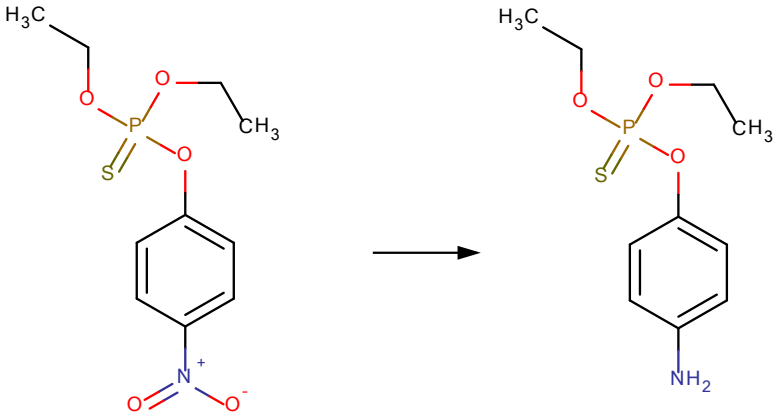
- 3-Bromo-5-nitrobenzene-1,2-diamine (Weber and Adams, 1995; Larson and Weber, 1994)



- 1,2,4,5-Tetrachloro-3-nitrobenzene (Macalady et al., 1986)



- O,O-diethyl O-4-nitrophenyl Phosphorothioate (Parathion) (Macalady et al., 1986)



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Weber, E.J.; Adams, R.L. Chemical- and Sediment-Mediated Reduction of the Azo Dye Disperse Blue 79. *Environ. Sci. Technol.* **1995**, *29*, 1163-1170.

Larson, R.A. and E.J. Weber. *Reaction Mechanisms in Environmental Organic Chemistry*. Boca Raton: CRC Press, Inc., 1994.

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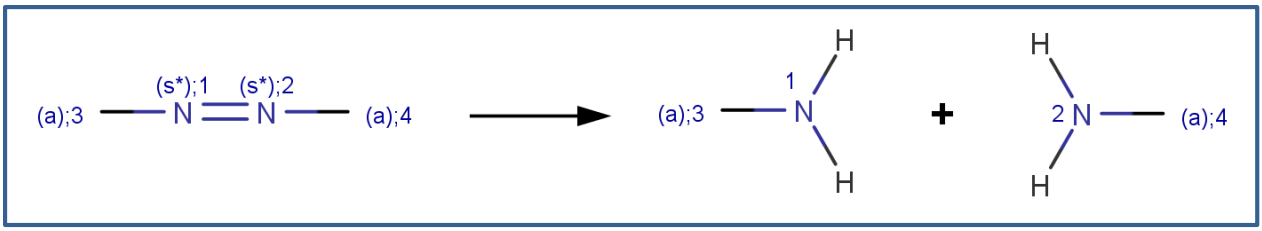
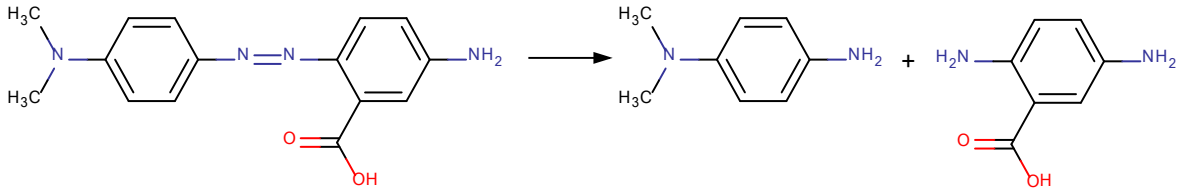
Aromatic Azo Reduction

SCHEME:

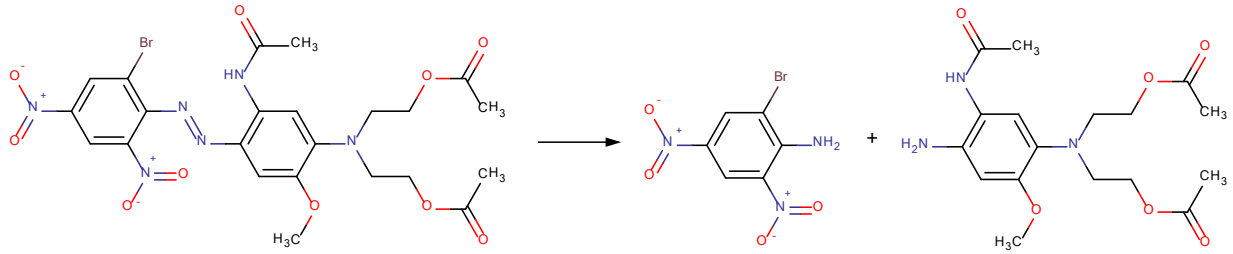


EXAMPLES:

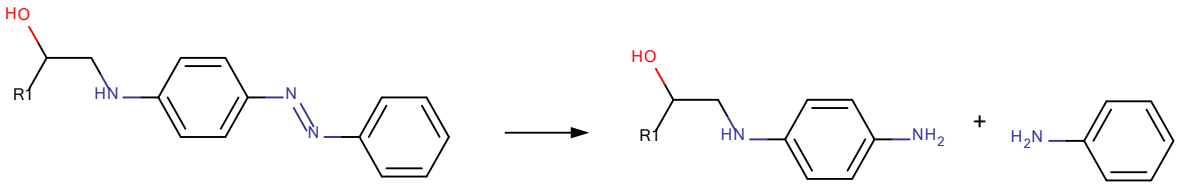
- 5-amino-2-{2-[4-(dimethylamino)phenyl]diazen-1-yl}benzoic acid (Weber and Wolfe, 1987)



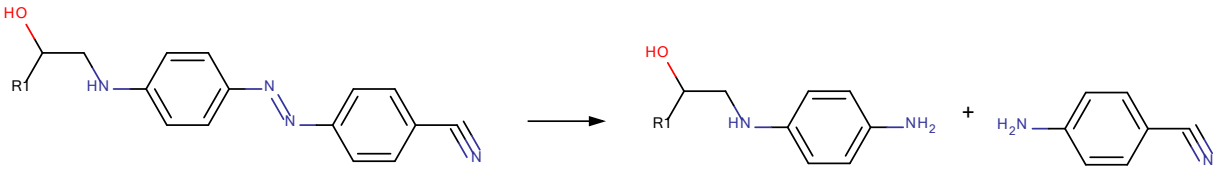
- Disperse Blue 79 (Weber and Adams, 1995; Larson and Weber, 1994)



- 1-({4-[(E)-2-phenyldiazen-1-yl]phenyl}amino)propan-2-ol (Substituted 4-Aminoazobenzene) (Weber, 1996)



- 4-[(E)-2-{4-[(2-hydroxypropyl)amino]phenyl}diazen-1-yl]benzonitrile (Substituted 4-cyano-4'-aminoazobenzene) (Zhang and Weber, 2009)



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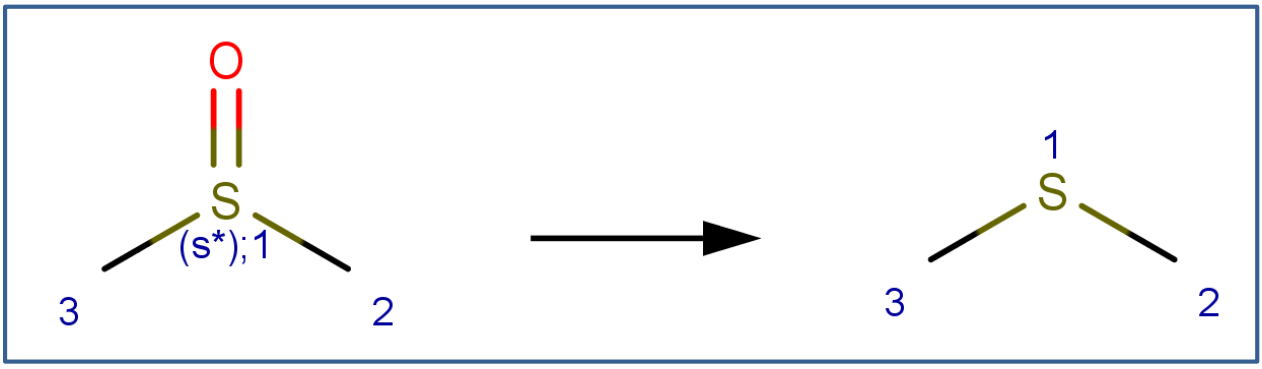
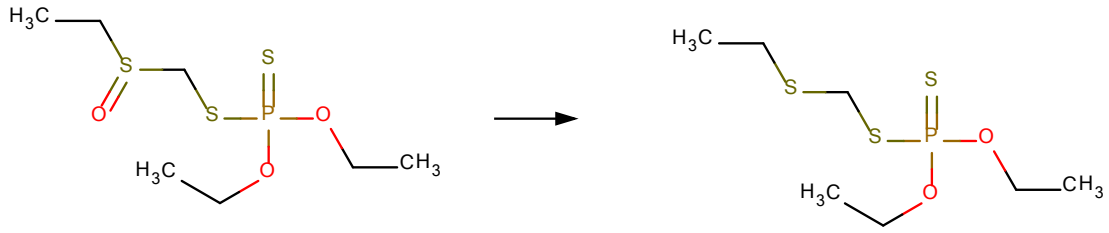
Sulfoxide Reduction

SCHEME:

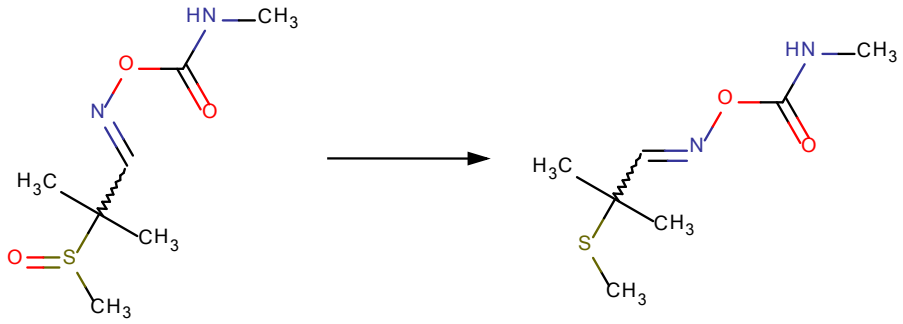


EXAMPLES:

- Phorate Sulfoxide (Larson and Weber, 1994)



- Aldicarb Sulfoxide (Larson and Weber, 1994)

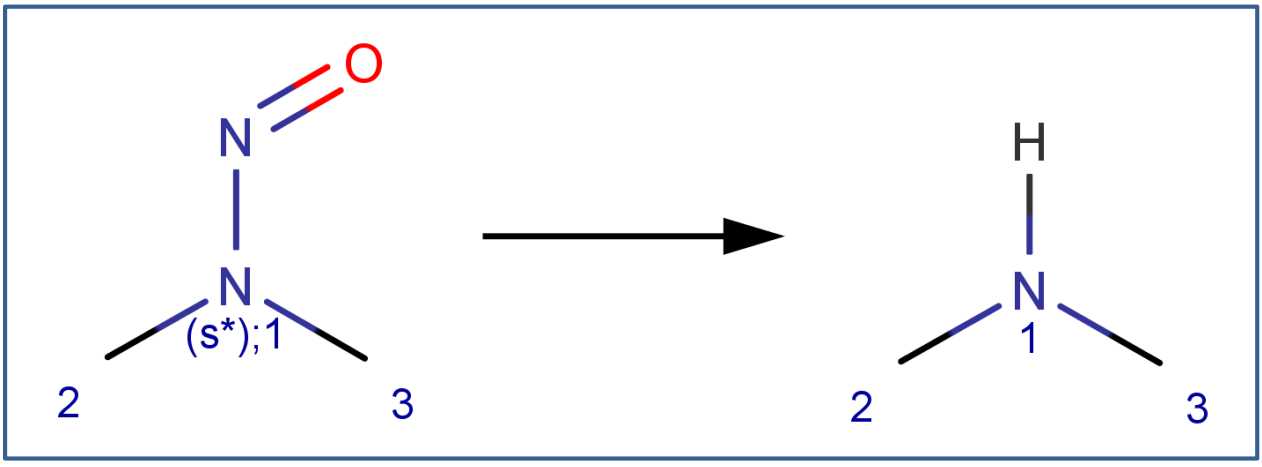


REFERENCES:

Larson, R.A. and E.J. Weber. *Reaction Mechanisms in Environmental Organic Chemistry*. Boca Raton: CRC Press, Inc., 1994.

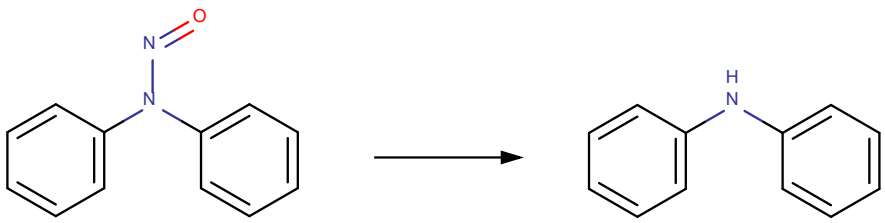
N-Nitrosoamine Reduction

SCHEME:

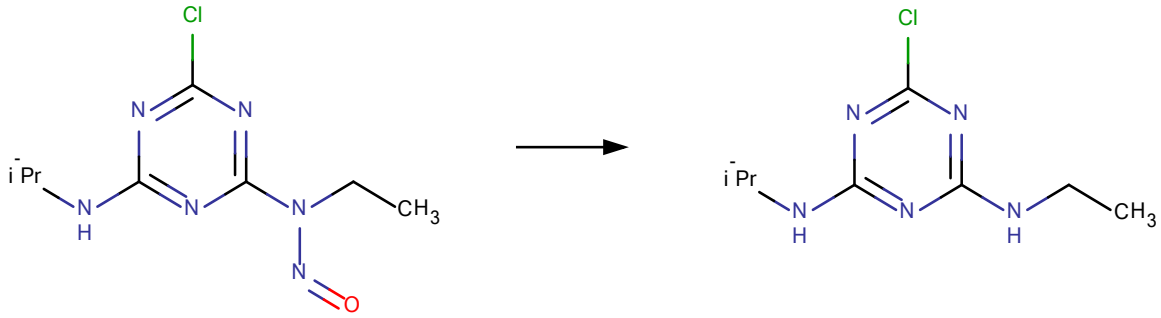


EXAMPLES:

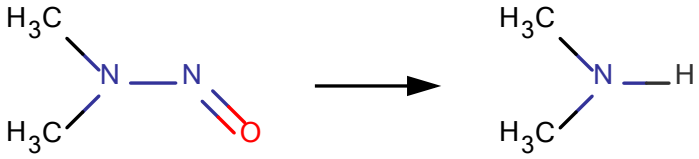
- Nitrosodiphenylamine (Larson and Weber, 1994)



- N-Nitrosoatrazine (Larson and Weber, 1994)



- Nitrosodimethylamine (Kulikova et al., 2009)



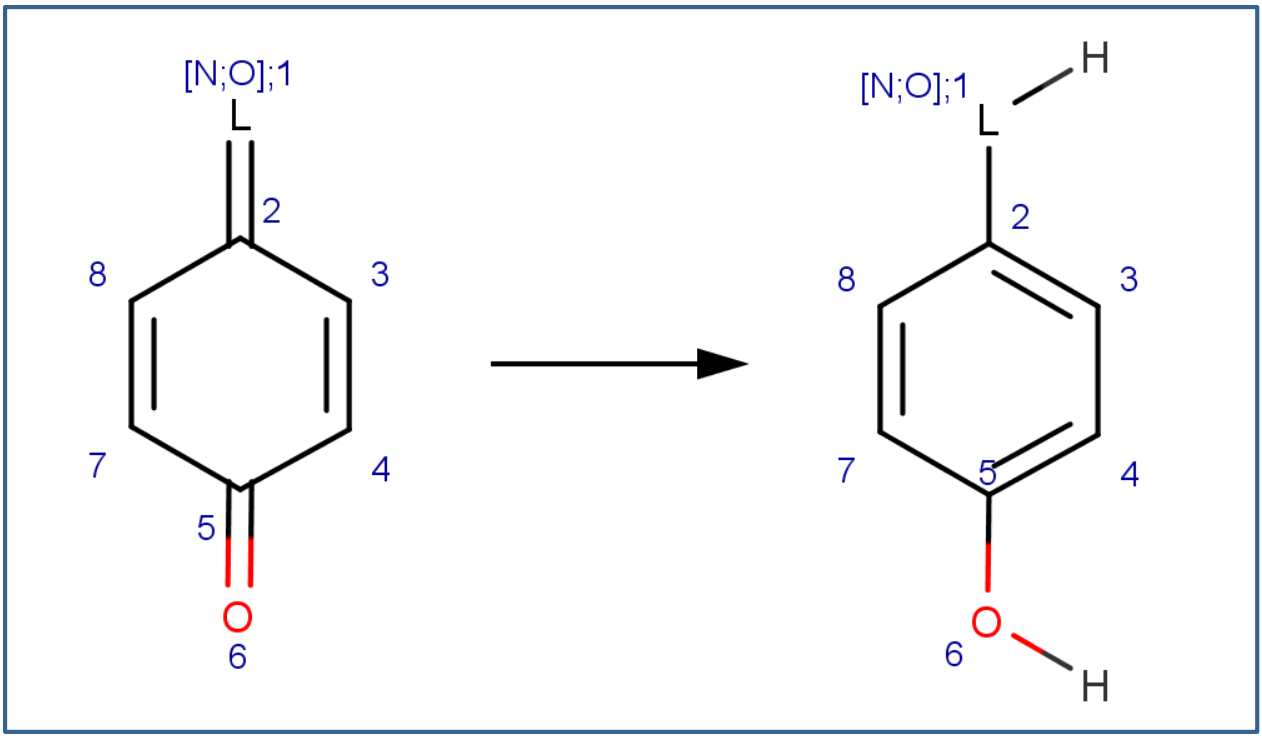
REFERENCES:

Larson, R.A. and E.J. Weber. *Reaction Mechanisms in Environmental Organic Chemistry*. Boca Raton: CRC Press, Inc., 1994.

Kulikova, N.; Baker, M.; Gabryelski, W. Collision induced dissociation of protonated N-nitrosodimethylamine by ion trap mass spectrometry: Ultimate carcinogens in gas phase. *Int. J. Mass Spec.* **2009**, *288*, 75-83.

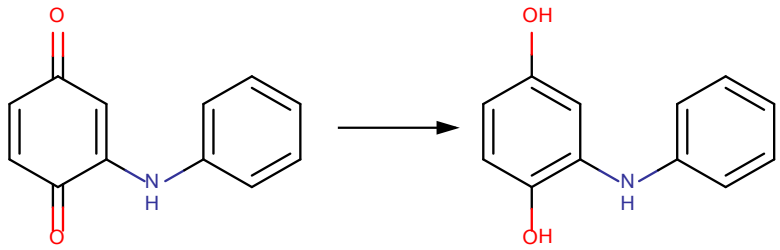
Quinone Reduction

SCHEME:

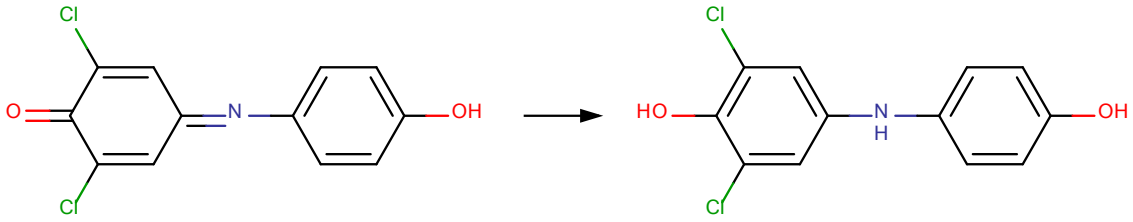


EXAMPLES:

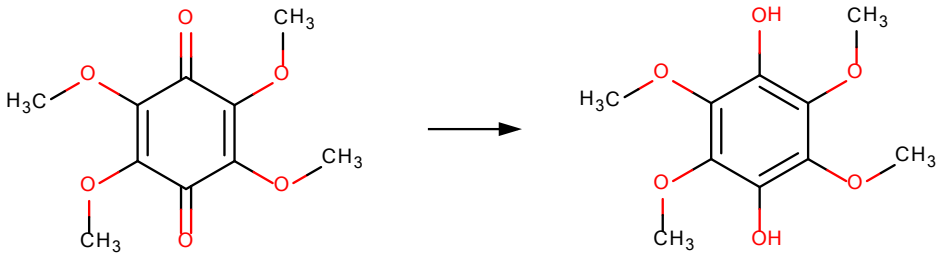
- Anilinohydroquinone (Colon et al., 2002)



- 2,6-dichlorophenolindophenol (Tonomura et al., 1978; Larson and Weber, 1994)



- Tetramethoxycyclohexa-2,5-diene-1,4-dione (Ref ??)



REFERENCES:

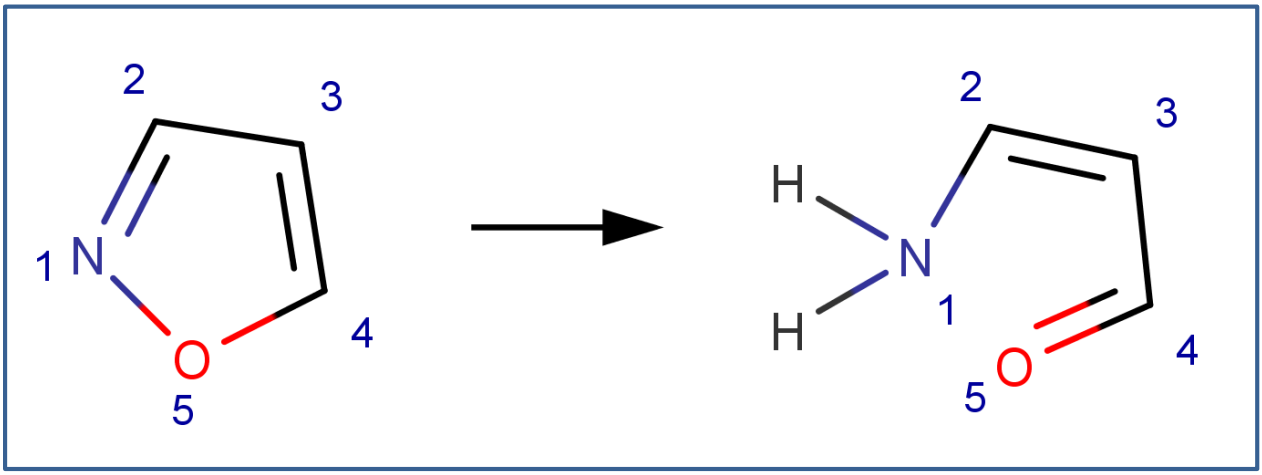
Colón, D.; Weber, E.J.; Baughman, G.L. Sediment-Associated Reactions of Aromatic Amines. 2. QSAR Development. *Environ. Sci. Technol.* **2002**, *36*, 2443-2450.

Tonomura, B.; Nakatani, H.; Ohnishi, M.; Yamaguchi-Ito, J.; Hiromi, K. Reduction for 2,6-Dichlorophenolindophenol and Potassium Ferricyanide by L-Ascorbic Acid. *Anal. Biochem.* **1978**, *84*, 370-383.

Larson, R.A. and E.J. Weber. *Reaction Mechanisms in Environmental Organic Chemistry*. Boca Raton: CRC Press, Inc., 1994.

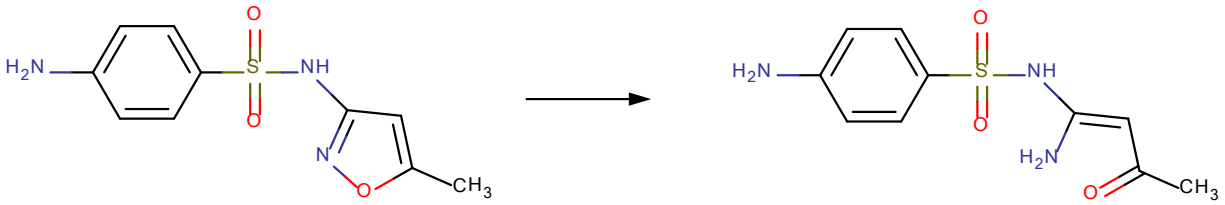
Isoxazole Cleavage

SCHEME:



EXAMPLES:

- Sulfamethoxazole (Mohatt et al., 2011)



REFERENCES:

Mohatt, J.L.; Hu, L.; Finneran, K.T.; Strathmann, T.J. Microbially Mediated Abiotic Transformation of the Antimicrobial Agent Sulfamethoxazole under Iron-Reducing Soil Conditions. *Environ. Sci. Technol.* **2011**, *45*, 4793-4801.

Abiotic Hydrolysis Reaction Library

Version 1.5 of the Abiotic Hydrolysis Reaction Library contains 17 reaction schemes:

- Halogenated Aliphatics: Nucleophilic Substitution
- Halogenated Aliphatics: Elimination
- Epoxide Hydrolysis
- Organophosphorus Ester Hydrolysis 1 (Base-Catalyzed)
- Organophosphorus Ester Hydrolysis 2 (Neutral or Acid-Catalyzed)
- Carboxylic Acid Ester Hydrolysis
- Lactone Hydrolysis
- Carbonate Hydrolysis
- Anhydride Hydrolysis
- Amide Hydrolysis
- Lactam Hydrolysis
- Carbamate Hydrolysis
- Urea Hydrolysis
- Sulfonylurea Hydrolysis
- Thiocarbamate Hydrolysis
- Nitrile Hydrolysis
- N-S Cleavage

Halogenated Aliphatics: Nucleophilic Substitution

SCHEME:

EXAMPLES:

- methyl bromide (EFSA, 2006; U.S. EPA, 1992)

- 1,3-dichloropropene (EFSA, 2004; Guo *et al*, 2004)

- 2-bromo-2,3-dimethylbutane (McMurry, 2011, p. 372)

- (R)-6-chloro-2,6-dimethyloctane (McMurry, 2011, p. 388)

- benzyl chloride (U.S. EPA, 1992)

REFERENCES:

EFSA (European Food Safety Authority), 2004. Draft Assessment Report (DAR): Initial risk assessment provided by the Member State Spain for the existing active substance 1,3-Dichloropropene of the second stage of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC, Volume 3, Annex B, part 5, B.8. Available from http://dar.efsa.europa.eu/dar-web/provision.

EFSA (European Food Safety Authority), 2006. Draft Assessment Report (DAR): Initial risk assessment provided by the Member State The United Kingdom for the existing active substance Methyl Bromide of the third stage (part A) of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC, Volume 3, Annex B, B.8. Available from http://dar.efsa.europa.eu/dar-web/provision.

Guo, M., S.K. Papiernik, W. Zhang and S.R. Yates. 2004. Effects of environmental factors of 1,3-dichloropropene hydrolysis in water and soil. *Journal of Environmental Quality*. 33(2): 612-618.

McMurry, J.E. 2011. *Organic Chemistry*, 8th ed. Boston, MA: Cengage Learning.

U.S. EPA (United States Environmental Protection Agency). 1992. Environmental fate constants for organic chemicals under consideration for EPA's Hazardous Waste Identification Rule. EPA/601/R-92/006.

Halogenated Aliphatics: Elimination

SCHEME:

This scheme includes two selectivity rules:

1. The carbon atom with the hydrogen leaving group (labeled reactant atom 2 in the scheme) is the one that has the most steric hindrance. In effect, this is Zaitsev's Rule, which states that "The alkene formed in greatest amount is the one that corresponds to removal of the hydrogen from the β-carbon having the fewest hydrogen substituents." (Reusch, 2010)
2. The order of removal of halogens (labeled reactant atom 3 in the scheme) is inverse to their atomic number, i.e., I>Br>Cl>F. This is due to the fact that the carbon-halogen bond strength is greatest for the most electrophilic halogen. (Larsen and Weber, 1994)

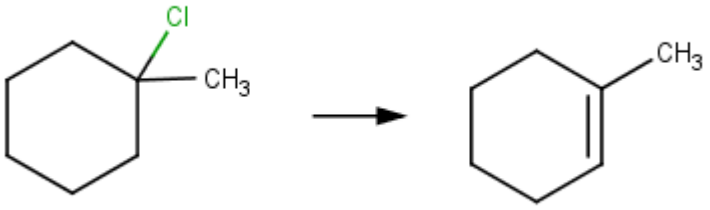
EXAMPLES:

- 2-bromo-2,3-dimethylbutane (McMurry, 2011, p. 372; Reusch, 2010)

- 2-bromobutane (McMurry, 2011, p. 397; Reusch, 2010)

- 2-bromo-2-methylbutane (McMurry, 2011, p. 397)

- 1-chloro-1-methylcyclohexane (McMurry, 2011, p. 399)



- DDD (dichlorodiphenyldichloroethane) (U.S. EPA, 1992)

- 1,2-dichloroethane (U.S. EPA, 1992; Miyamoto and Urano, 1996)

- 1,1,2,2-tetrachloroethane (Cooper *et al*, 1987)

- 1,1,1-trichloroethane (Cline and Delfino, 1989; Gerkens and Franklin, 1989; Miyamoto and Urano, 1996)

- 1,2-dibromo-3-chloropropane (Burlinson *et al*, 1982)

REFERENCES:

Burlinson, N.E., L.A. Lee and D.H. Rosenblatt. 1982. Kinetics and products of hydrolysis of 1,2-dibromo-3-chloropropane. *Environmental Science and Technology*. 16(9): 627-632.

Cline, P.V. and J.J. Delfino. 1989. Transformation kinetics of 1,1,1-trichloroethane to the stable product 1,1-dicheloroethene. *In* Larsen, R.A., editor, *Biohazards of Drinking Water Treatment*. Lewis Publishers, Inc., Chelsea, Michigan, pp. 47-56.

Cooper, W.J., M. Mehran, D.J. Riusech and J.A. Joens. 1987. Abiotic transformation of halogenated organics: 1. Elimination reaction of 1,1,2,2-tetrachloroethane and formation of 1,1,2-trichloroethene. *Environmental Science and Technology*. 21(11): 1112-1114.

Gerkens, R.R. and J.A. Franklin. 1989. The rate of degradation of 1,1,1-trichloroethane in water by hydrolysis and dehydrochlorination. *Chemosphere*. 19(12): 1929-1937.

McMurry, J.E. 2011. *Organic Chemistry*, 8th ed. Boston, MA: Cengage Learning.

Miyamoto, K. and K. Urano. 1996. Reaction rates and intermediates and chlorinated organic compounds in water and soil. *Chemosphere*. 32(12): 2399-2408.

Reusch, W.H. 2010. *Virtual Textbook of Organic Chemistry*. http://www2.chemistry.msu.edu/faculty/reusch/VirtTxtJml/intro1.htm.

U.S. EPA (United States Environmental Protection Agency). 1992. Environmental fate constants for organic chemicals under consideration for EPA's Hazardous Waste Identification Rule. EPA/601/R-92/006.

Epoxide Hydrolysis

SCHEME:

EXAMPLES:

- 1,2-Epoxycyclohexane (McMurry, 2011)

- Epichlorohydrin (Gaca *et al*, 2011)

- Endrin (Larsen and Weber, 1994; U.S. EPA, 1992)

- 1,2-Epoxy-1,2,3,4-tetrahydronaphthalene (Becker *et al*, 1979)

REFERENCES:

Becker, A.R., J.M. Janusz and T.C. Bruice. 1979. Solution chemistry of the *syn*- and *anti*-tetrahydrodiol epoxides, the *syn*- and *anti*-tetrahydrodimethoxy epoxides, and the 1,2- and 1,4-tetrahydro epoxides of naphthalene. *Journal of the American Chemical Society*. 101(19): 5679-5687.

Gaca, J., G. Wejnerowska and P. Cysewski. 2011. Mechanism of the acidic hydrolysis of epichlorohydrin. *Journal of Physical Organic Chemistry*. 24: 1045-1050.

Larson, R.A. and E.J. Weber. *Reaction Mechanisms in Environmental Organic Chemistry*. Boca Raton: CRC Press, Inc., 1994.

McMurry, J.E. 2011. *Organic Chemistry*, 8th ed. Boston, MA: Cengage Learning.

U.S. EPA (United States Environmental Protection Agency). 1992. Environmental fate constants for organic chemicals under consideration for EPA's Hazardous Waste Identification Rule. EPA/601/R-92/006.

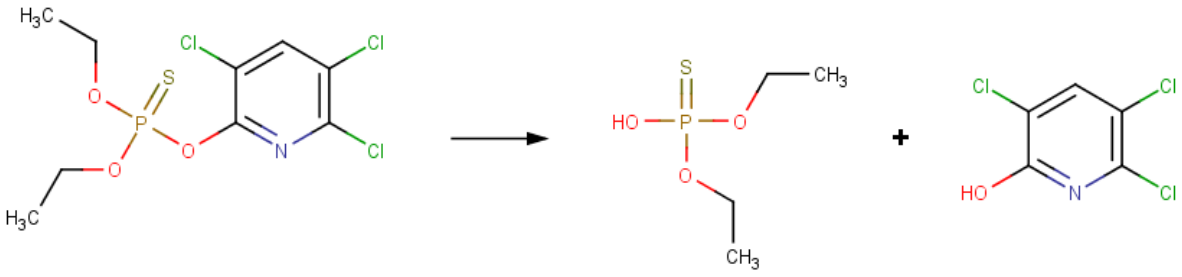
Organophosphorus Ester Hydrolysis 1 (Base-Catalyzed)

SCHEME:

This scheme includes a selectivity rule to identify the most likely leaving group. Base-catalyzed cleavage favors P-L cleavage (where L is O, S, or N) at the L group that is attached to the most electron-withdrawing group (Larson and Weber, 1994). The selectivity rule specifies that the leaving group (labeled atom 3) is the attached the carbon atom (labeled atom 4) with the highest electrophilicity.

EXAMPLES:

- Chlorpyrifos (Macalady and Wolfe, 1983)



- Dimethoate (EFSA, 2005a)

- Fenamiphos (EFSA, 2005b)

- Fenitrothion (EFSA, 2005c; Greenhalgh *et al* , 1980)

Organophosphorus Ester Hydrolysis 2 (Neutral and Acid-Catalyzed)

SCHEME:

This scheme includes a selectivity rule to identify the most likely leaving group. Neutral and acid-catalyzed cleavage favors L-C cleavage (where L is O, S, or N), but not at the L group that is attached to the most electron-withdrawing group (Larson and Weber, 1994). The selectivity rule specifies that the leaving group (labeled atom 4) is the carbon atom with the lowest electrophilicity.

EXAMPLES:

- Chlorpyrifos (Macalady and Wolfe, 1983)

- Dimethoate (EFSA, 2005a)

- Fenitrothion (EFSA, 2005c; Greenhalgh *et al* , 1980)

-

REFERENCES:

EFSA (European Food Safety Authority), 2005a. Draft Assessment Report (DAR): Initial risk assessment provided by the Member State the United Kingdom for the existing active substance Dimethoate of the second stage of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC, Volume 3, Annex B, B.8. Available from http://dar.efsa.europa.eu/dar-web/provision.

EFSA (European Food Safety Authority), 2005b. Draft Assessment Report (DAR): Initial risk assessment provided by the Member State the Netherlands for the existing active substance Fenamiphos of the second stage of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC, Volume 3, Annex B, B.8. Available from http://dar.efsa.europa.eu/dar-web/provision.

EFSA (European Food Safety Authority), 2005c. Draft Assessment Report (DAR): Initial risk assessment provided by the Member State the United Kingdom for the existing active substance Fenitrothion of the second stage of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC, Volume 3, Annex B, B.8. Available from http://dar.efsa.europa.eu/dar-web/provision.

Greenhalgh, R. K.L. Dhawan and P. Weinberger. 1980. Hydrolysis of fenitrothion in model and natural aquatic systems. *Journal of Agricultural and Food Chemistry*. 28(1): 102-105.

Larson, R.A. and E.J. Weber. *Reaction Mechanisms in Environmental Organic Chemistry*. Boca Raton: CRC Press, Inc., 1994.

Macalady, D.L. and N.L. Wolfe. 1983. New perspectives on the hydrolytic degradation of the organophosphorothioate insecticide chlorpyrifos. *Journal of Agricultural and Food Chemistry*. 31(6): 1139-1147.

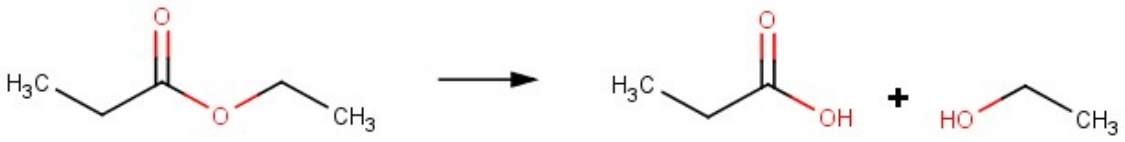
Carboxylic Acid Ester Hydrolysis

SCHEME:

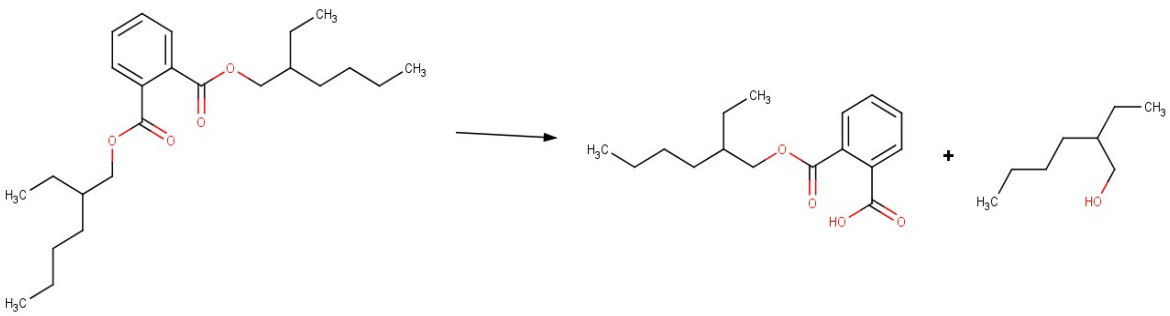
Two reactivity rules are included for this scheme. To distinguish this scheme from the Anhydride Hydrolysis scheme, the first reactivity rule specifies that atom 3 is not part of an anhydride structural fragment. To distinguish this scheme from the Lactone scheme, the second reactivity rule specifies that atom 3 is a chain atom.

EXAMPLES:

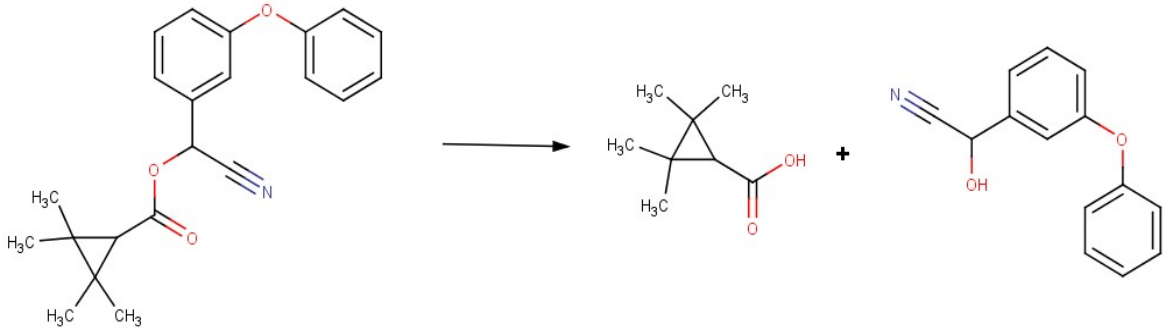
- Ethyl propanoate (McMurry, 2012)



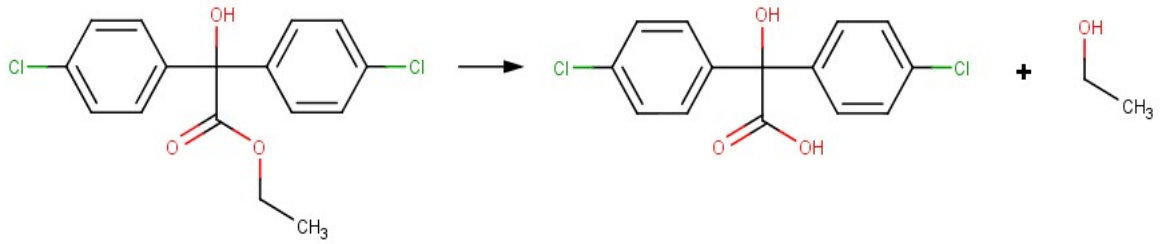
- Bis(2-ethylhexyl)phthalate (Larson and Weber, 1994)



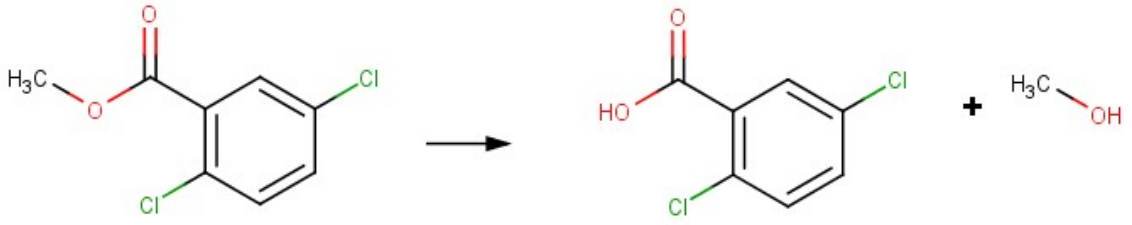
- Fenpropathrin (Larson and Weber, 1994)



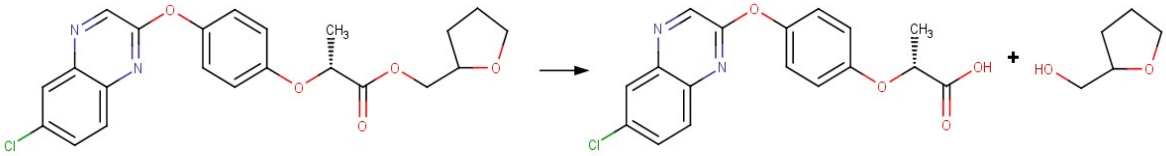
- Chlorobenzilate (Larson and Weber, 1994)



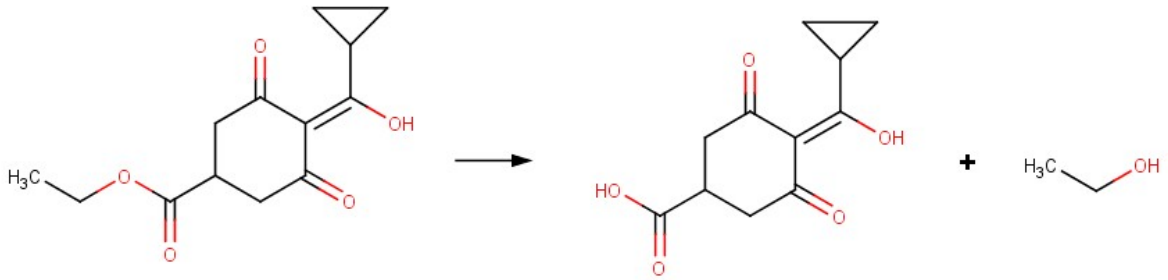
- 2,5-dichlorobenzoic acid methylester (EFSA, 2007a)



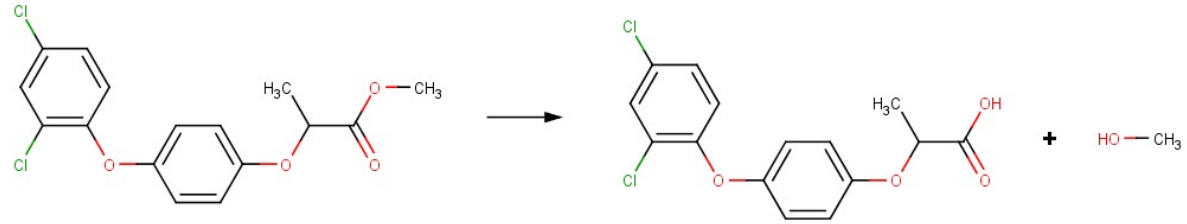
- Propaquizafop (EFSA, 2006)



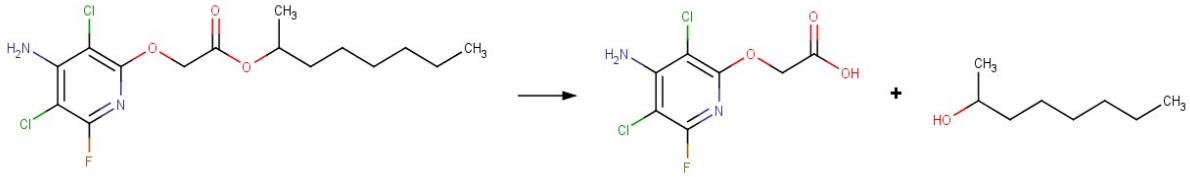
- Trinexapac (EFSA, 2005)



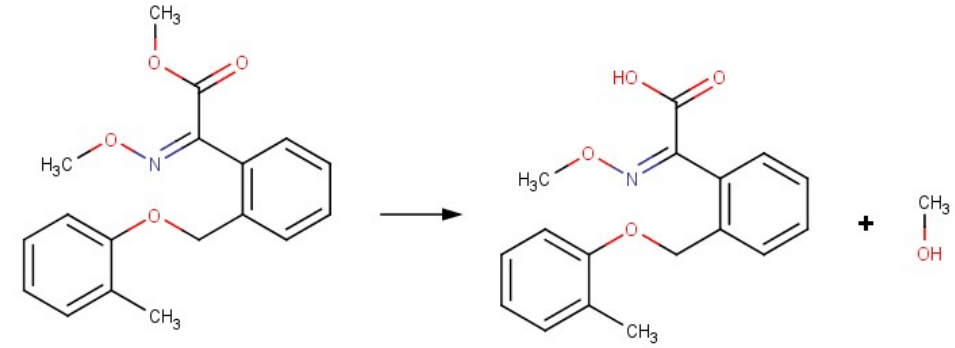
- Diclofop-methyl (EFSA, 2007b)



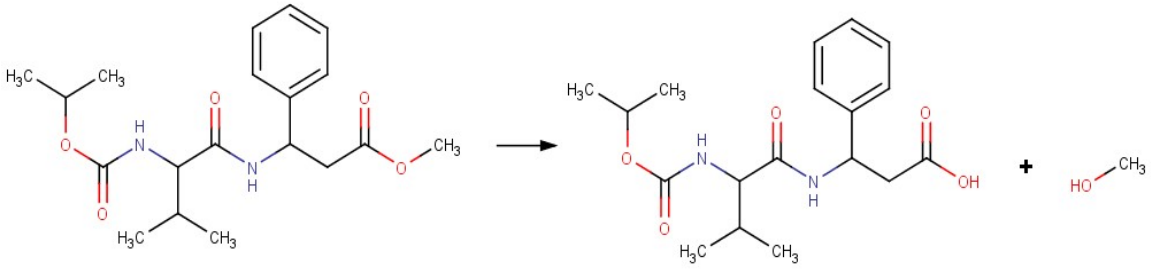
- Fluroxypyr (EFSA, 2009)



- Kresoxim-methyl (EFSA, 2010)



- Valifenalate (EFSA, 2012)



REFERENCES:

Larson, R.A. and E.J. Weber. *Reaction Mechanisms in Environmental Organic Chemistry*. Boca Raton: CRC Press, Inc., 1994.

McMurry, J.E. 2011. *Organic Chemistry*, 8th ed. Boston, MA: Cengage Learning.

EFSA (European Food Safety Authority), 2005. Draft Assessment Report (DAR): Initial risk assessment provided by the Member State the Netherlands for the existing active substance Trinexapac of the second stage of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC, Volume 3, Annex B, B.7, part 1. Available from http://dar.efsa.europa.eu/dar-web/provision.

EFSA (European Food Safety Authority), 2006. Draft Assessment Report (DAR): Initial risk assessment provided by the Member State Italy for the existing active substance Propaquizafop of the third stage (part A) of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC, Volume 3, Annex B, B.8. Available from http://dar.efsa.europa.eu/dar-web/provision.

EFSA (European Food Safety Authority), 2007a. Draft Assessment Report (DAR): Initial risk assessment provided by the Member State Germany for the existing active substance Dichlorobenzoic Acid Methylester of the third stage (part B) of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC, Volume 3, Annex B, part 2, B.6. Available from http://dar.efsa.europa.eu/dar-web/provision.

EFSA (European Food Safety Authority), 2007b. Draft Assessment Report (DAR): Initial risk assessment provided by the Member State France for the existing active substance Diclofop-Methyl of the third stage (part A) of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC, Volume 3, Annex B, part 4, B.8. Available from http://dar.efsa.europa.eu/dar-web/provision.

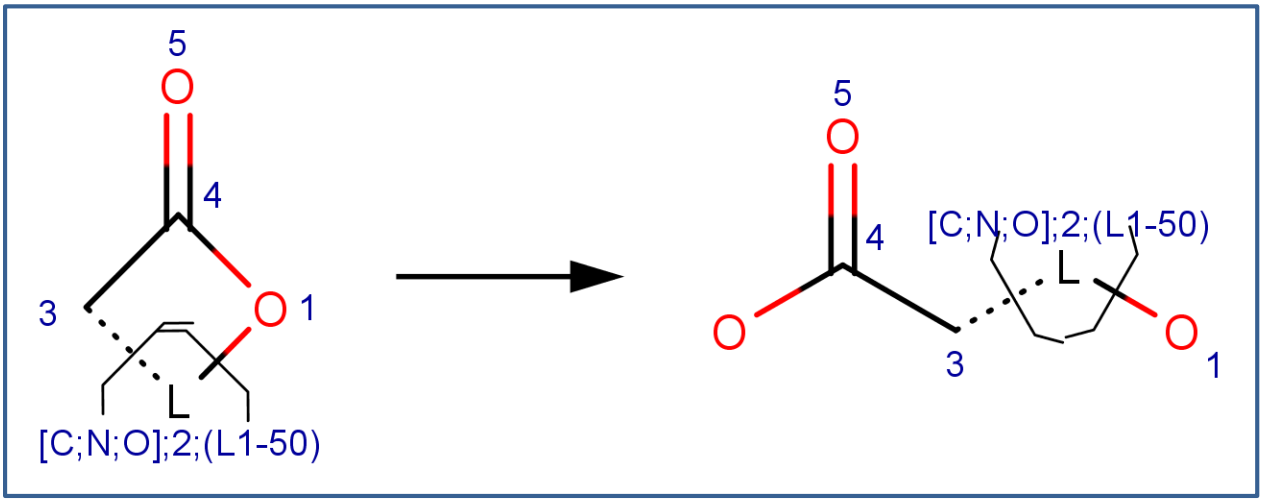
EFSA (European Food Safety Authority), 2009. Draft Assessment Report (DAR): Initial risk assessment provided by the Member State Ireland for the existing active substance Fluroxypyr upon submission in the framework of the renewal of the inclusion of a first group of active substances in Annex I to Council Directive 91/414/EEC in accordance with Commission Regulation (EC) No 737/2007, Volume 3, B7. http://dar.efsa.europa.eu/dar-web/provision.

EFSA (European Food Safety Authority), 2010. Draft Assessment Report (DAR): Initial risk assessment provided by the Member State Belgium for the existing active substance Kresoxim-Methyl of the third stage (part A) of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC, Volume 3, Annex B, B.8. Available from http://dar.efsa.europa.eu/dar-web/provision.

EFSA (European Food Safety Authority), 2012. Draft Assessment Report (DAR): Initial risk assessment provided by the Member State Hungary for the existing active substance Valifenalate of the third stage (part A) of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC, Volume 3, Annex B, B.8. Available from http://dar.efsa.europa.eu/dar-web/provision.

Lactone Hydrolysis

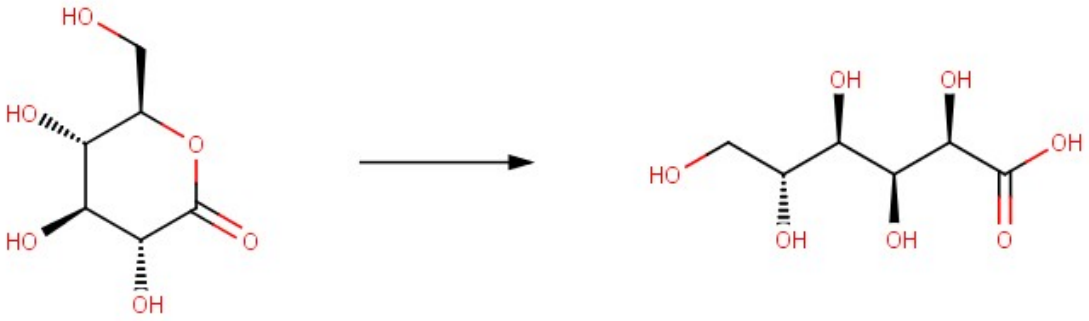
SCHEME:



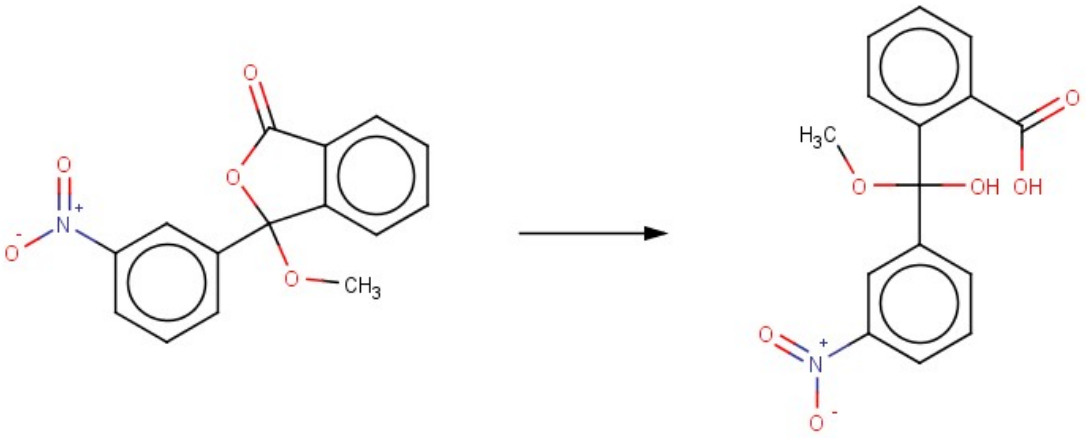
To distinguish this scheme from the Carboxylic Acid Ester scheme, apply a reactivity rule which specifies that atom 1 is a ring atom. Additionally, to distinguish this scheme from hydrolysis of cyclic anhydrides, apply a reactivity rule which specifies that atom 1 is not part of an anhydride structural fragment.

EXAMPLES:

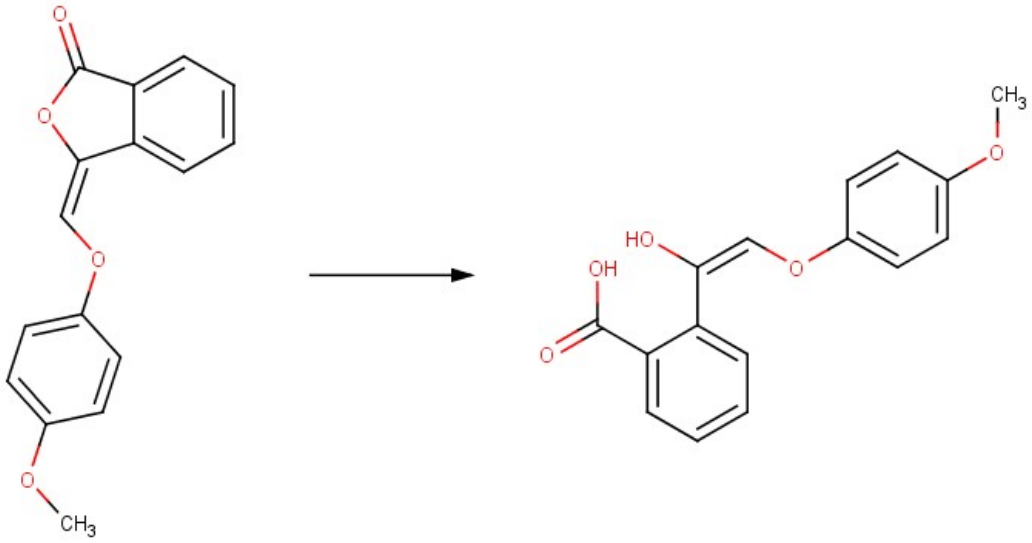
- Gluconolactone (Pocker and Green, 1973)



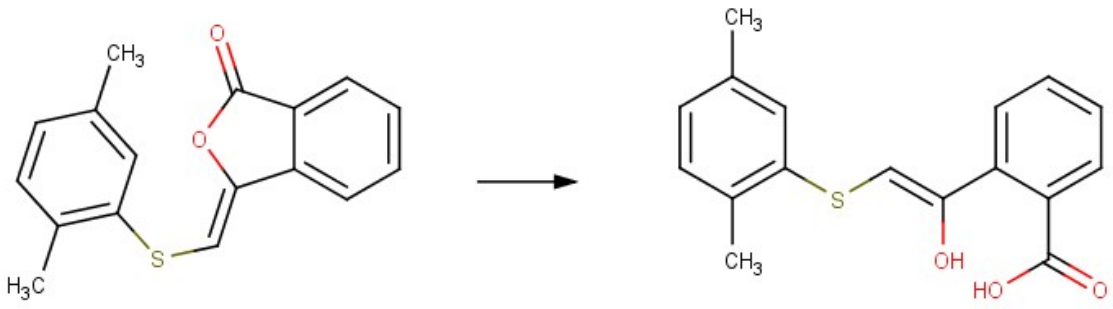
- 3-methoxy-3-(3-nitrophenyl)-2-benzofuran-1-one (Weeks and Whitney, 1981)



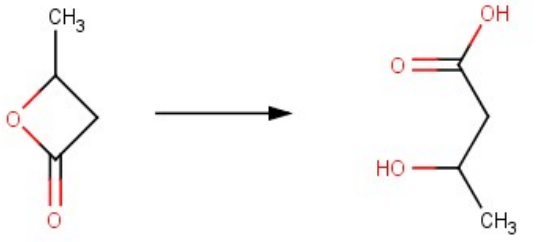
- (3E)-3-(4-methoxyphenoxymethylidene)-2-benzofuran-1-one (Bowden *et al*, 1998)



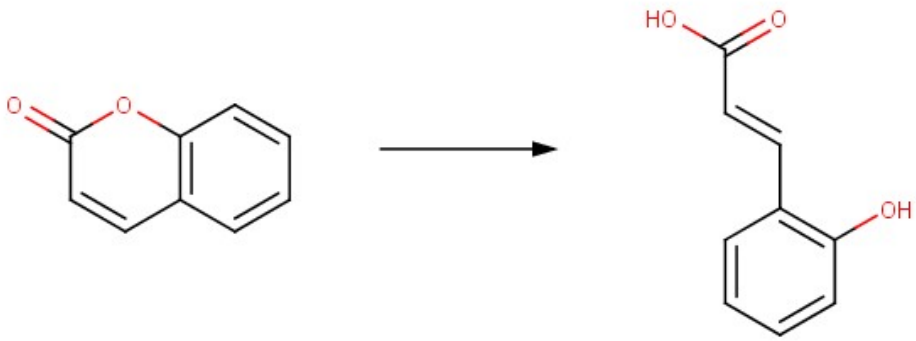
- (3Z)-3-{[(2,5-dimethylphenyl)sulfanyl]methylidene}-2-benzofuran-1-one (Bowden *et al*, 1998)



- Beta-butyrolactone (Olson and Voule, 1951)



- Coumarin (El-Khatib and Nassr, 2007)



REFERENCES:

Bowden, K.; R.J. Ranson, A. Perjessy, M. Lacova, O. Hritzova, and W.W.F. Fabian. 1998. Base-catalyzed hydrolysis of gamma-lactones: reactivity-structure correlations for 3-(substituted phenoxy and thiophenoxymethylene)-(Z)-1(3H)-isobenzofuranones. *J. Phys. Org. Chem.* 11: 467-474.

El-Khatib, R.M. and L.A.M.E. Nassr. 2007. Reactivity trends of the base hydrolysis of coumarin and thiocoumarin in binary aqueous-methanol mixtures at different temperatures. *Spectrochimica Acta Part A.* 67: 643-648.

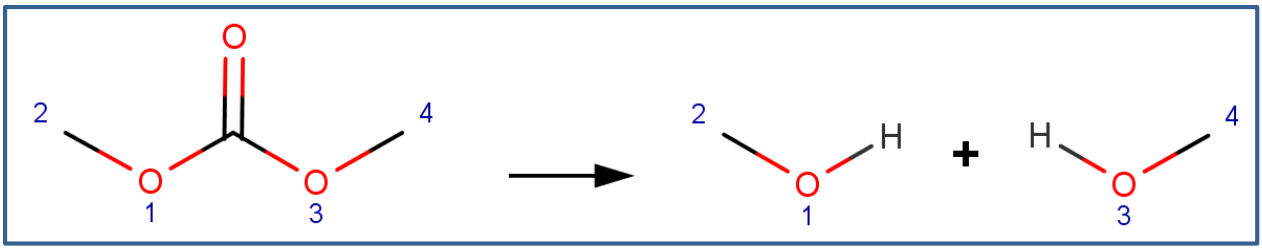
Olson, A.R. and P.V. Volue. 1951. The Hydrolysis of Beta-Butyrolactone. *J. Am. Chem. Soc.* 73: 2468-2471.

Pocker, Y. and E. Green. 1973. Hydrolysis of D-glucono-delta-lactone. I. General Acid-Base Catalysis, Solvent Deuterium Isotope Effects, and Transition State Characterization. *J. Am. Chem. Soc.* 95: 113-119.

Weeks, D.P. and D.B. Whitney. 1981. Hydrolysis of 3-(m-nitrophenyl)-3-methoxyphthalide. *J. Am. Chem. Soc.* 103: 3555-3558.

Carbonate Hydrolysis

SCHEME:



Note that a selectivity rule is included for this scheme to eliminate duplication of products. Specifically, to distinguish between the carbon atoms labelled 1 and 3, atom 1 is identified as the less sterically hindered atom.

EXAMPLES:

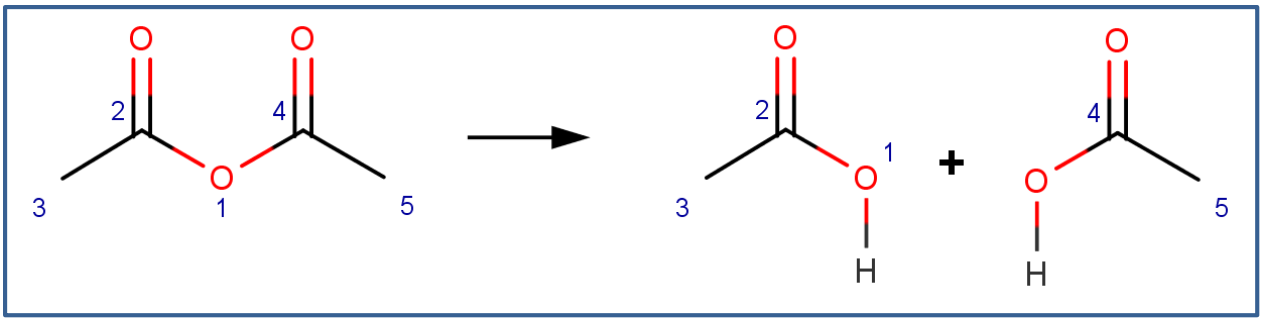
- Spirotetramat (EFSA, 2008)

REFERENCES:

EFSA (European Food Safety Authority). 2008. Draft Assessment Report (DAR): Joint Review Project/ OECD Monograph on Spirotetramat provided by the regulatory authorities of Austria, Canada and the United States of America, Volume 3, Annex B, B.8. Available from http://dar.efsa.europa.eu/dar-web/provision.

Anhydride Hydrolysis

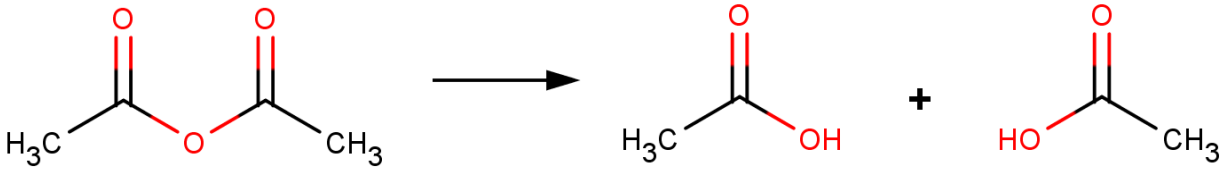
SCHEME:



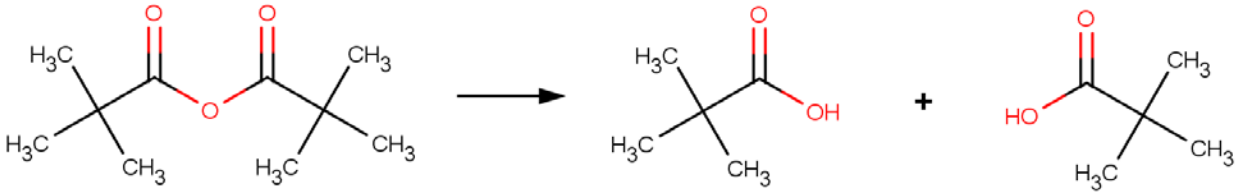
Note that a selectivity rule is included for this scheme to eliminate duplication of products. Specifically, to distinguish between the carbon atoms labelled 2 and 4, atom 2 is identified as the less sterically hindered atom.

EXAMPLES:

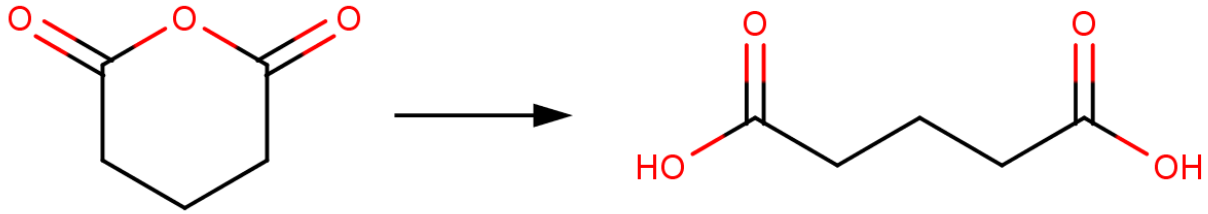
- Acetic anhydride (Bunton and Fendler, 1965)



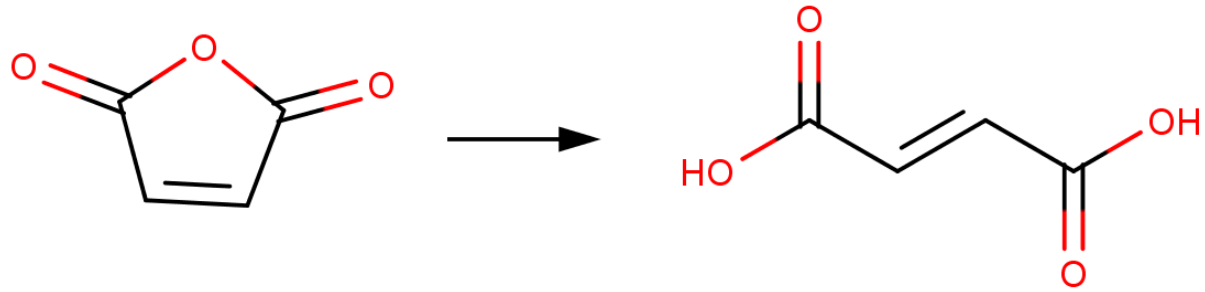
- Trimethylacetic anhydride (Bunton and Fendler, 1965)



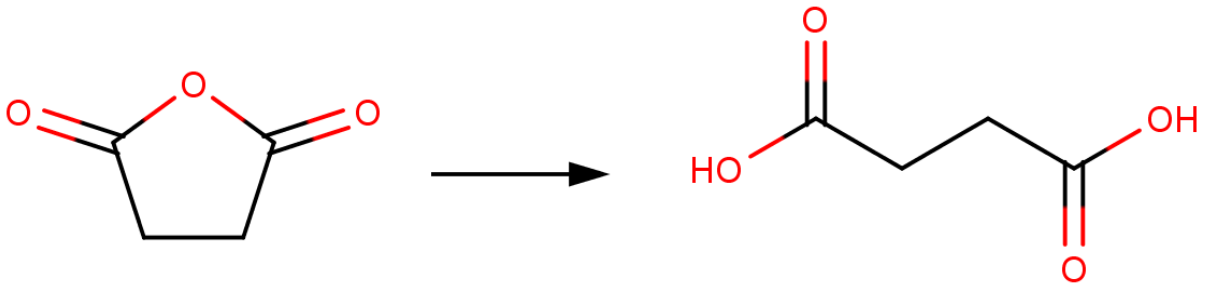
- Glutaric anhydride (Bunton *et al*, 1963)



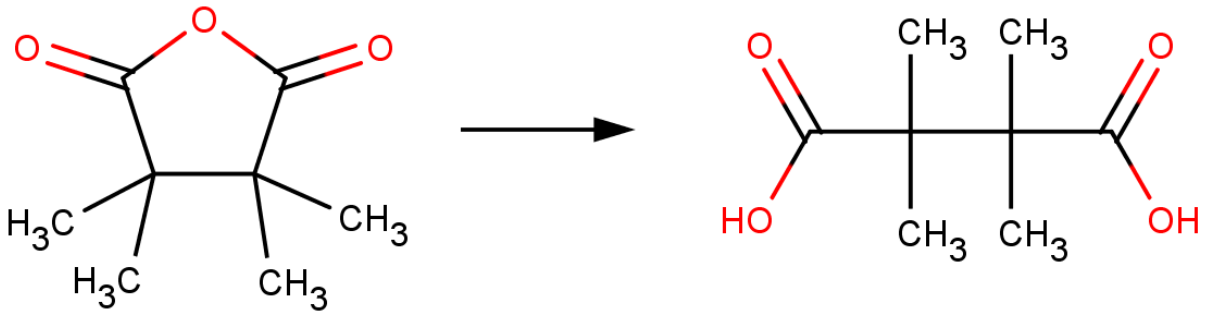
- Maleic anhydride (Bunton *et al*, 1963)



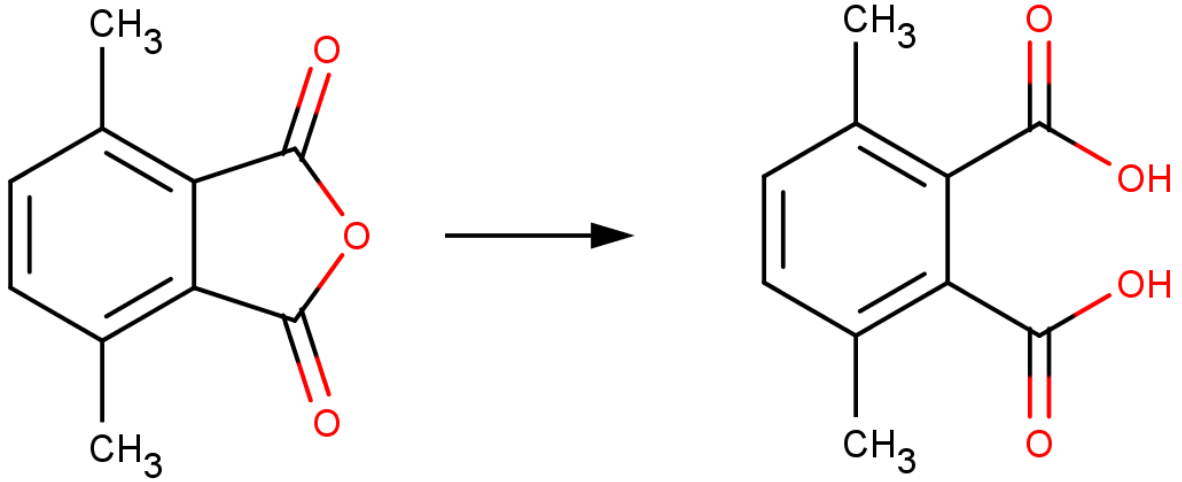
- Succinic anhydride (Bunton *et al*, 1963)



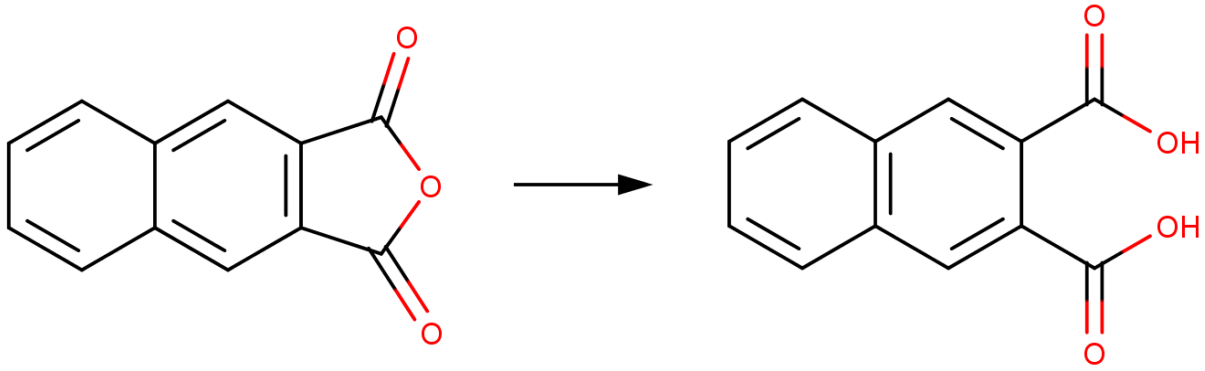
- Tetramethylsuccinic anhydride (Bunton *et al*, 1963)



- 3,6-Dimethylphthalic anhydride (Hawkins, 1975a,b)



- Naphtho(2,3-c)furan-1,3-dione (Barros *et al*, 2001)



REFERENCES:

Barros, T.C., S. Yunes, G. Menegon, F. Nome, H. Chaimovich, M.J. Politi, L.G. Dias and I.M. Cuccovia. 2001. Hydrolysis of 1,8- and 2,3-naphthalic † anhydrides and the mechanism of cyclization of 1,8-naphthalic acid in aqueous solutions. *Journal of the Chemical Society, Perkin Transactions 2*. 2001(12): 2342-2350.

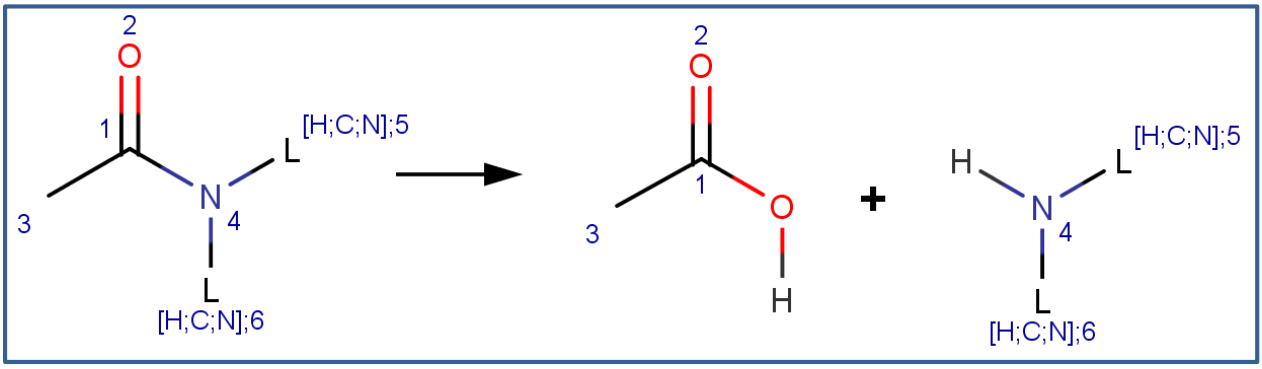
Bunton, C.A. and J.H. Fendler. 1965. The hydrolysis of carboxylic anhydrides. V. The acid hydrolysis of acetic and trimethylacetic anhydride. *Journal of Organic Chemistry*. 30(5): 1365-1371.

Bunton, C.A., N.A. Fuller, S.G. Perry and V.J. Shiner. 1963. The hydrolysis of carboxylic anhydrides. Part III. Reactions in initially neutral solution. *Journal of the Chemical Society*. 1963: 2918-2926.

Hawkins M.D. 1975. Hydrolysis of phthalic and 3,6-dimethylphthalic anhydrides. *Journal of the Chemical Society, Perkin Transactions 2*. 1975(4): 282-284.

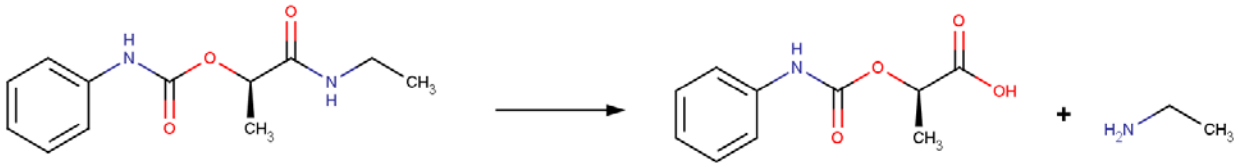
Hawkins M.D. 1975b. Hydrolysis of 2,2,2-trifluoroethyl hydrogen 3,6-dimethylphthalate. *Journal of the Chemical Society, Perkin Transactions 2*. 1975(4): 285-287.

Amide Hydrolysis



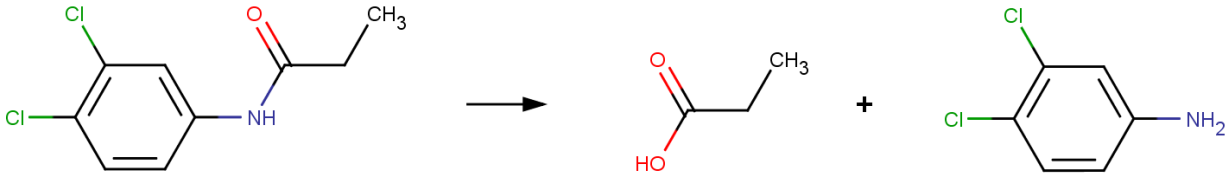
EXAMPLES:

- Carbetamide (EFSA, 2006a)



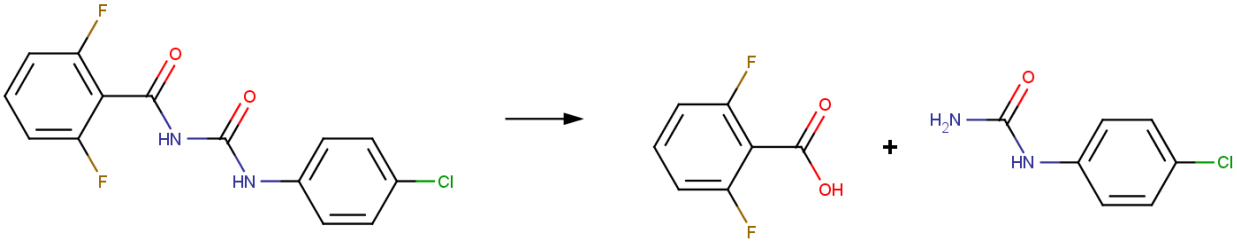
- Pronamide (Larson and Weber, 1994)

- Propanil (EFSA, 2008b)

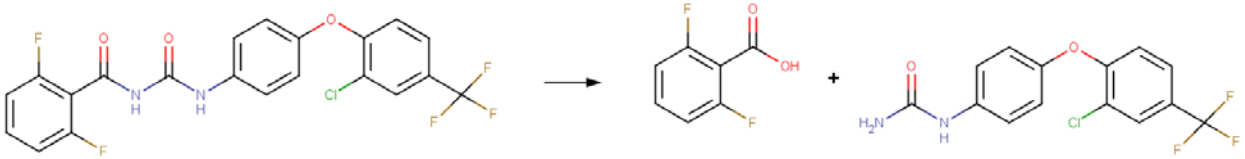


FORMYLUREA EXAMPLES: (Urea group adjacent to an amide group)

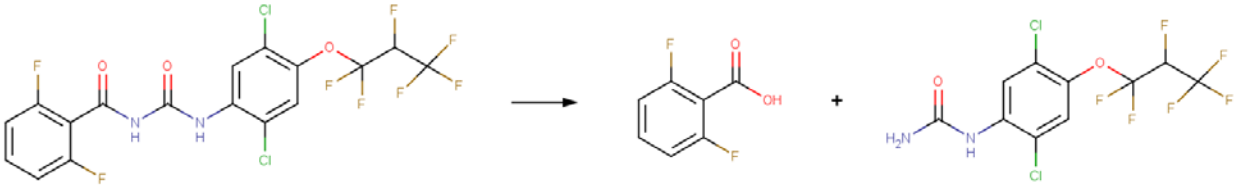
- Diflubenzuron (EFSA, 2006b)



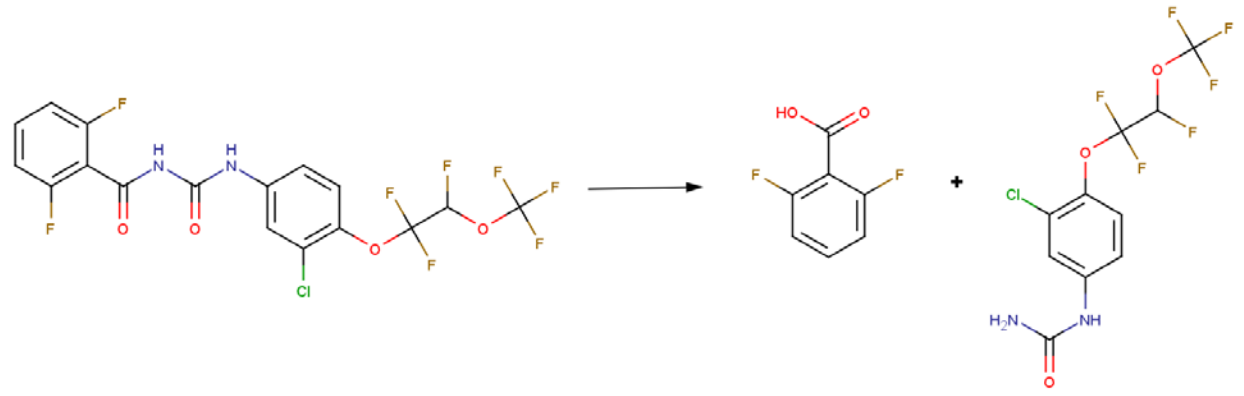
- Flufenoxuron (EFSA, 2008a)



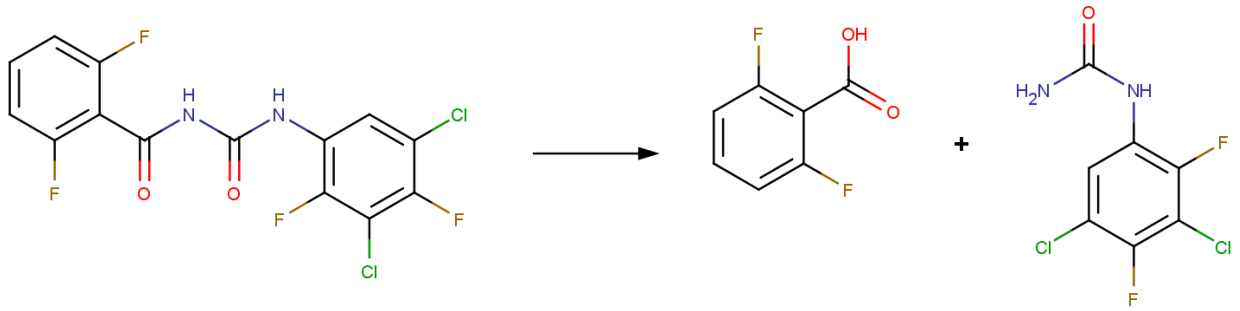
- Lufenuron (EFSA, 2007b)



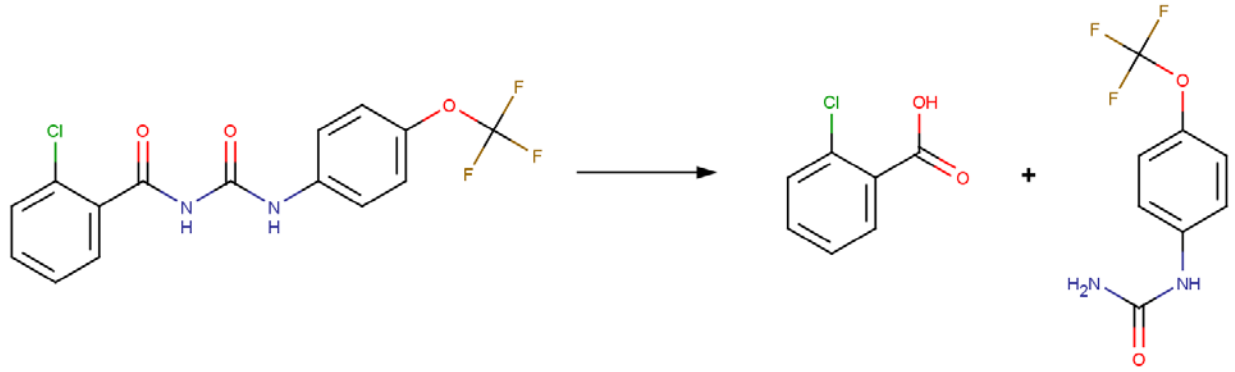
- Novaluron (EFSA, 2008c)



- Teflubenzuron (EFSA, 2007c)



- Triflumuron (EFSA, 2007a)



REFERENCES:

EFSA (European Food Safety Authority), 2006a. Draft Assessment Report (DAR): Initial risk assessment provided by the Member State France for the existing active substance Carbetamide of the third stage (part A) of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC, Volume 3, Annex B, part 4, B.8. Available from http://dar.efsa.europa.eu/dar-web/provision.

EFSA (European Food Safety Authority), 2006b. Draft Assessment Report (DAR): Initial risk assessment provided by the Member State Sweden for the existing active substance Diflubenzuron of the third stage (part A) of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC, Volume 3, Annex B, B.2 and B.8. Available from http://dar.efsa.europa.eu/dar-web/provision.

EFSA (European Food Safety Authority). 2007a. Draft Assessment Report (DAR): Initial risk assessment provided by the Member State Italy for the existing active substance Triflumuron of the third stage (part A)

of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC, Volume 3, Annex B, part 4, B.8. Available from http://dar.efsa.europa.eu/dar-web/provision.

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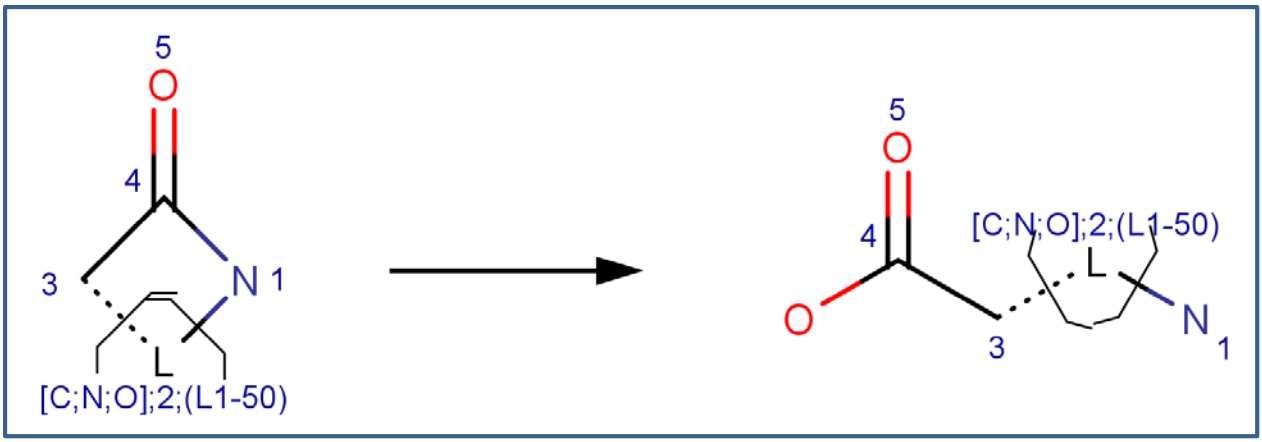
EFSA (European Food Safety Authority), 2008c. Draft Assessment Report (DAR): Initial risk assessment provided by the Member State the United Kingdom for the existing active substance Novaluron of the review programme referred to in Article 8(1) of Council Directive 91/414/EEC, Volume 3, Annex B, part 4, B.8. Available from http://dar.efsa.europa.eu/dar-web/provision.

Larson, R.A. and E.J. Weber. *Reaction Mechanisms in Environmental Organic Chemistry*. Boca Raton: CRC Press, Inc., 1994.

Lactam Hydrolysis

SCHEME:

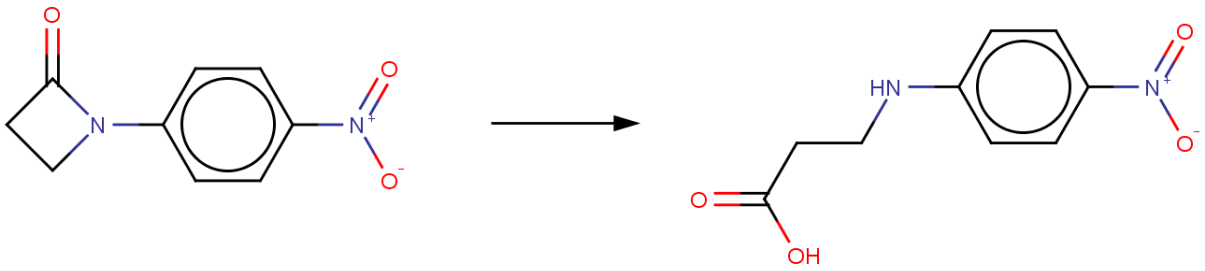


To distinguish this scheme from the Amide scheme, apply a reactivity rule which specifies that atom 1 is a ring atom. Additionally, to distinguish this scheme from hydrolysis of cyclic imides, apply a reactivity rule which specifies that atom 1 is not part of an imide structural fragment.

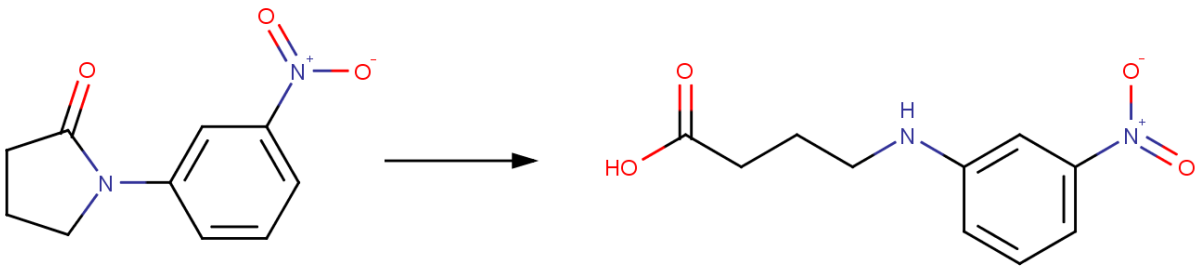
The lactam hydrolysis pathway is unlikely to be a significant transformation process under environmentally relevant conditions. In abiotic hydrolysis studies at 25°C, the products of the lactam hydrolysis pathway are generally not observed. However, at high temperature (> 50°C) and/or elevated concentrations of OH^-, significant formation of the products of the lactam hydrolysis pathway has been observed (e.g., Abbas *et al*, 1996; Blackburn and Plackett, 1972; Bowden and Bromley, 1990). Additionally, studies comparing the rates of hydrolysis of lactam rings of various sizes indicate that the four-member β-lactam ring is more susceptible to hydrolysis than larger ring sizes (Bowden and Bromley, 1990; Imming *et al*, 2000; Wan *et al*, 1980).

EXAMPLES:

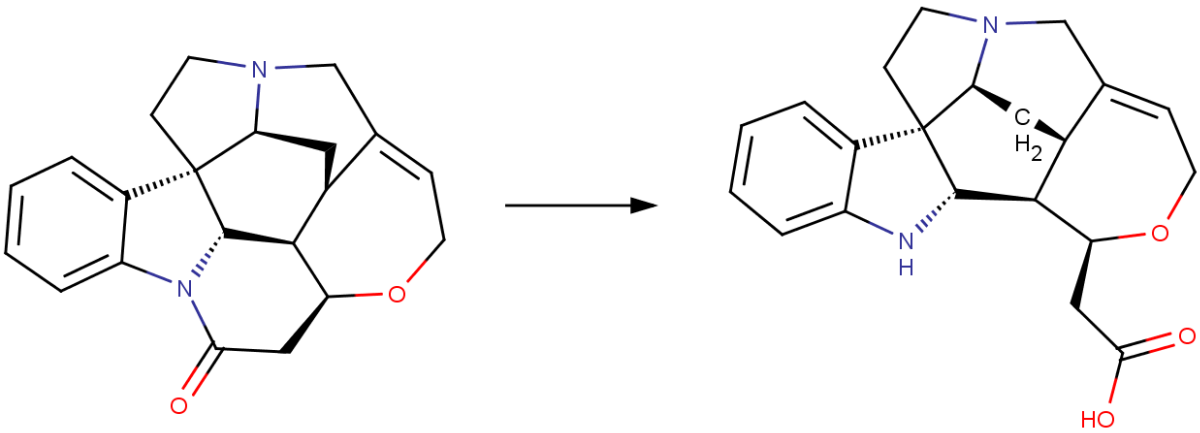
- 1-(4-Nitrophenyl)-2-azetidinone (Blackburn and Plackett, 1972)



- 1-(3-Nitrophenyl)-2-pyrrolidinone (Bowden and Bromley, 1990)



- Strychnine (Abbas *et al*, 1996)



REFERENCES:

Abbas, K.A., P.Hurst and J.T. Edward. 1996. Reexamination of the Kirkwood-Westheimer theory of electrostatic effects. V. Effect of charged substituents on the rates of alkaline hydrolysis of substituted strychnines. *Canadian Journal of Chemistry*. 75: 441-448.

Blackburn, G.M. and J.D. Plackett. 1972. Strain effects in acyl transfer reactions. Part 1. The kinetics of hydrolysis of some N-aryl-lactams. *Journal of the Chemical Society, Perkin Transactions 2*. 1972(10): 1366-1371.

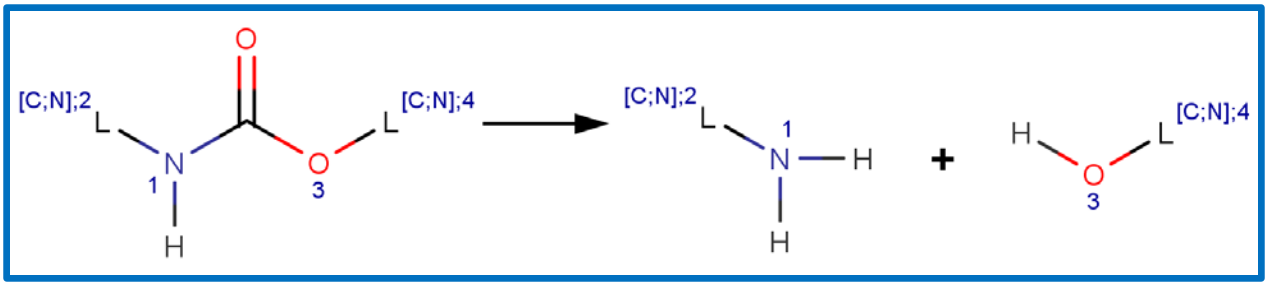
Bowden, K. and K. Bromley. 1990. Reactions of carbonyl compounds in basic solutions. Part 14. The alkaline hydrolysis of substituted N-Methylformanilides, N-Methylacetanilides, 1-Phenylazetidin-2-ones, 1-Phenyl-2-pyrrolidones, and 1-Phenyl-2-piperidones. *Journal of the Chemical Society, Perkin Transactions 2*. 1990(12): 2103-2109.

Imming, P., B. Klar and D. Dix. 2000. Hydrolytic stability versus ring size in lactams: Implications for the development of lactam antibiotics and other serine protease inhibitors. *Journal of Medicinal Chemistry*. 43(22): 4328-4331.

Wan, P., T.A. Modro and K. Yates. 1980. The kinetics and mechanism of acid catalysed hydrolysis of lactams. *Canadian Journal of Chemistry*. 58: 2423-2432.

Carbamate Hydrolysis

SCHEME:



As is shown in the examples below, a number of N-alkyl and N-aryl carbamates have been observed to undergo the hydrolysis scheme shown above. The N,N-di-substituted carbamates (a.k.a. secondary carbamates) are resistant to hydrolysis (Aly and El-Dib, 1971; Christenson, 1964; EFSA, 2004c; Larson and Weber, 1994; Wolfe et al. 1978a).

EXAMPLES:

- 4-nitrophenyl N-methylcarbamate (Bender and Homer, 1965)

- Carbaryl (a.k.a. Sevin) (Aly and El-Dib, 1971; EFSA, 2005a; Wolfe *et al*, 1978b)

- Propoxur (a.k.a. Baygon) (Aly and El-Dib, 1971)

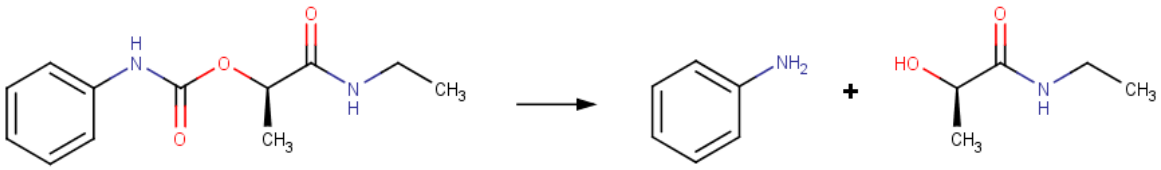
- Carbofuran (EFSA, 2004a; Iesce *et al*, 2006)

- Methiocarb (EFSA, 2005b)

- Methomyl (EFSA, 2004b)

- Carbendazim (EFSA, 2009)

- Carbetamide (EFSA, 2006)



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Aly, O.M. and M.A. El-Dib. 1971. Studies on the Persistence of Some Carbamate Insecticides in the Aquatic Environment. *Water Research*. *5*: 1191-1205.

Bender, M.L. and R.B. Homer. 1965. The mechanism of the alkaline hydrolysis of *p*-nitrophenyl N-methylcarbamate. *Journal of Organic Chemistry*. 30(11): 3975-3978.

Christenson, I. 1964. Alkaline hydrolysis of some carbamic acid esters. *Acta Chemica Scandinavica*. 18(4): 904-922.

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EFSA (European Food Safety Authority), 2004b. Draft Assessment Report (DAR): Initial risk assessment provided by the Member State United Kingdom for the existing active substance Methomyl of the second stage of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC, Volume 3, Annex B, B.6. Available from http://dar.efsa.europa.eu/dar-web/provision.

EFSA (European Food Safety Authority), 2004c. Draft Assessment Report (DAR): Initial risk assessment provided by the Member State United Kingdom for the existing active substance Pirimicarb of the second stage of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC, Volume 3, Annex B, B.8. Available from http://dar.efsa.europa.eu/dar-web/provision.

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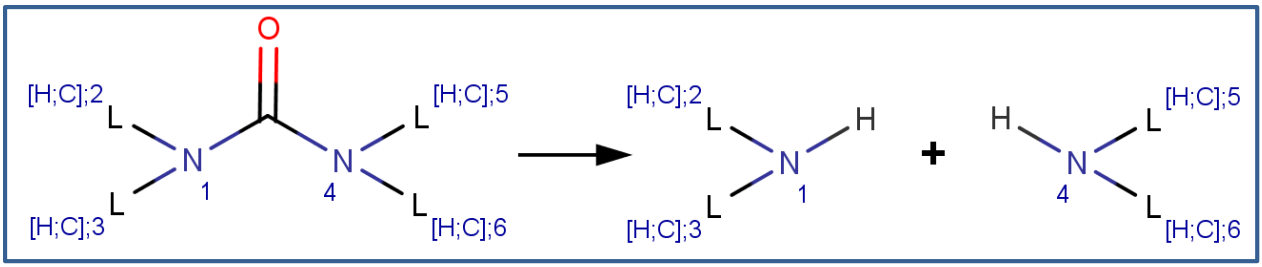
Urea Hydrolysis

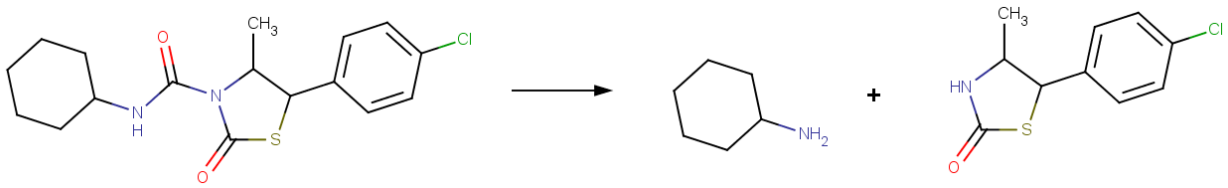
SCHEME:



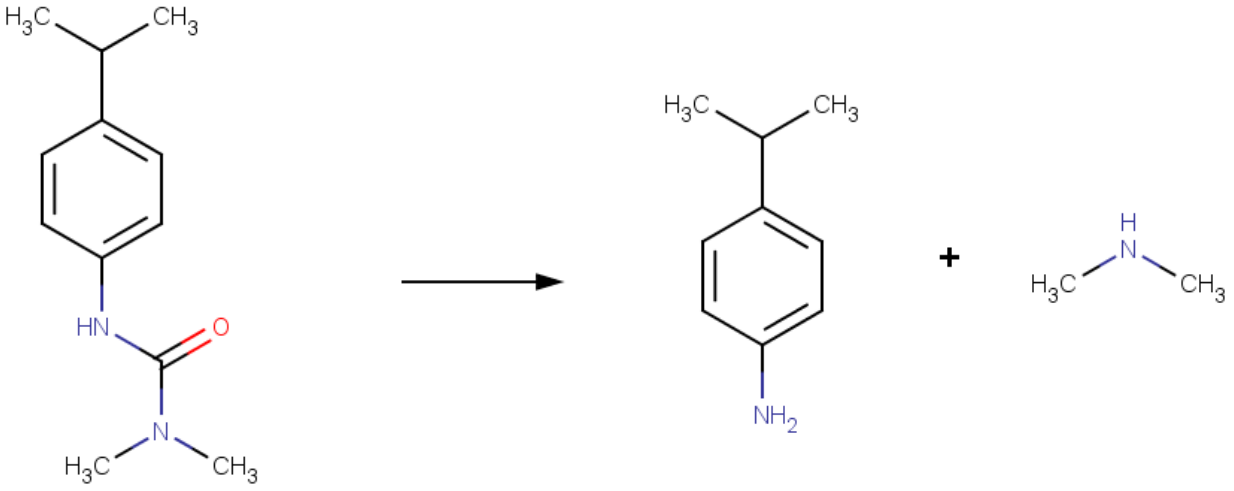
The urea hydrolysis pathway is unlikely to be a significant transformation process under environmentally relevant conditions. In abiotic hydrolysis studies at 25°C, the products of the urea hydrolysis pathway are generally either minor products (<3%) or not observed at all. For example, in molecules with a urea group adjacent to an amide group, hydrolysis is observed to follow the amide pathway (formylurea examples). However, at high temperature (> 50°C), significant formation of the products of the urea hydrolysis pathway has been observed (EFSA, 2006a; EFSA, 2006b; EFSA, 2014). Additionally, the urea hydrolysis pathway may occur through an enzyme-mediated process.

EXAMPLES:

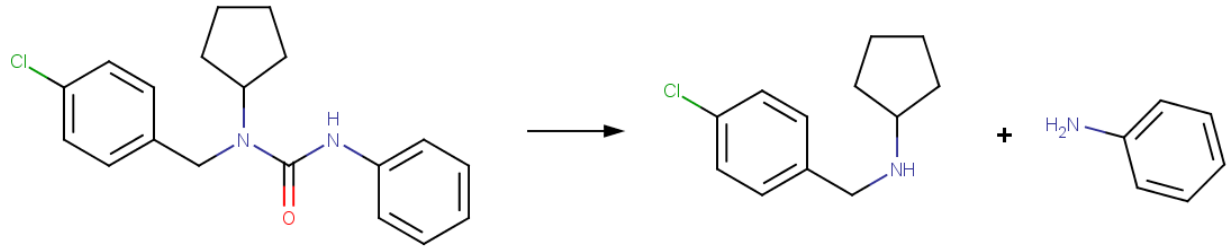
- Hexythiazox (EFSA, 2006a)



- Isoproturon (EFSA, 2014; Penning *et al*, 2008)



- Pencycuron (EFSA, 2006b)



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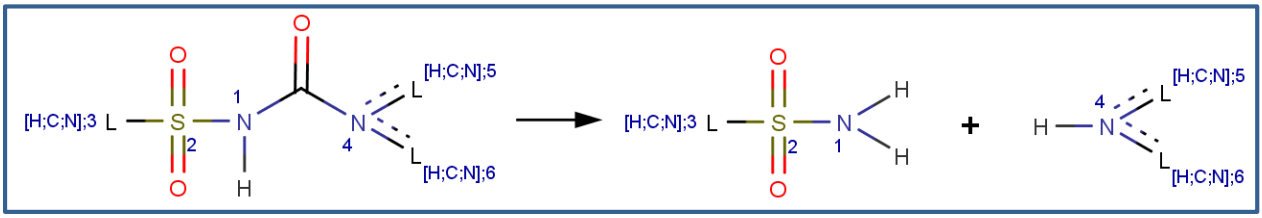
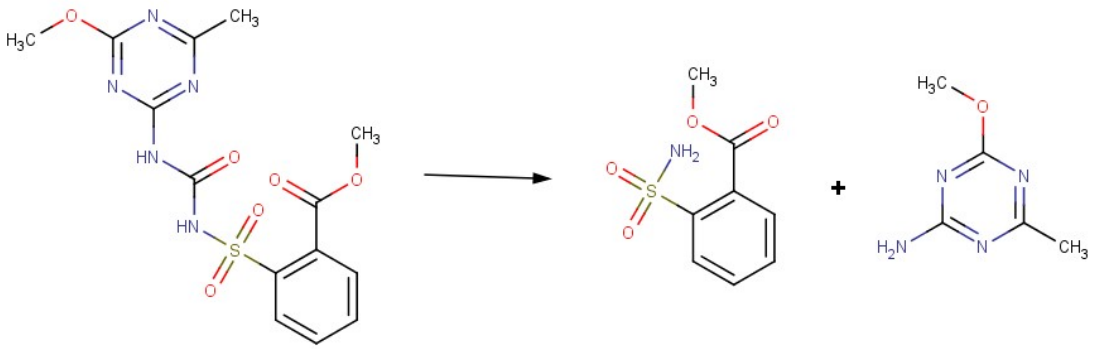
Sulfonylurea Hydrolysis

SCHEME:

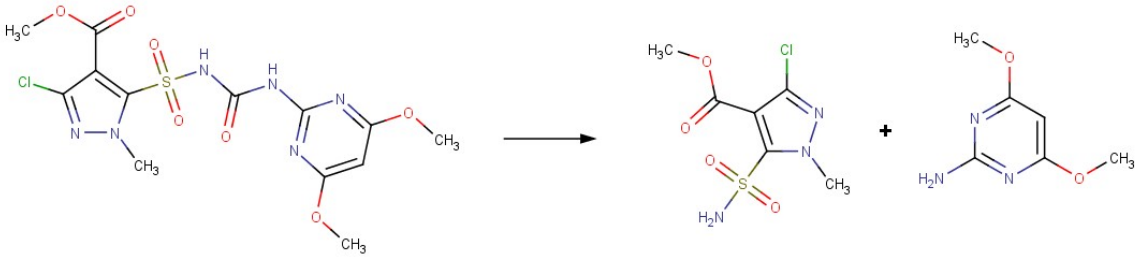


EXAMPLES:

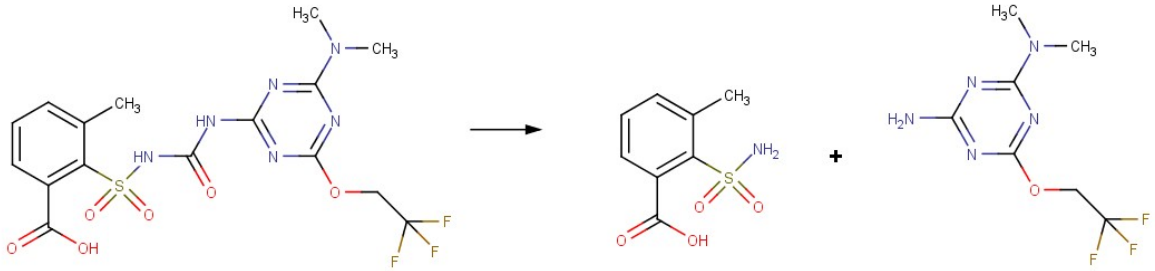
- Metsulfuron-methyl (EFSA, 2013)



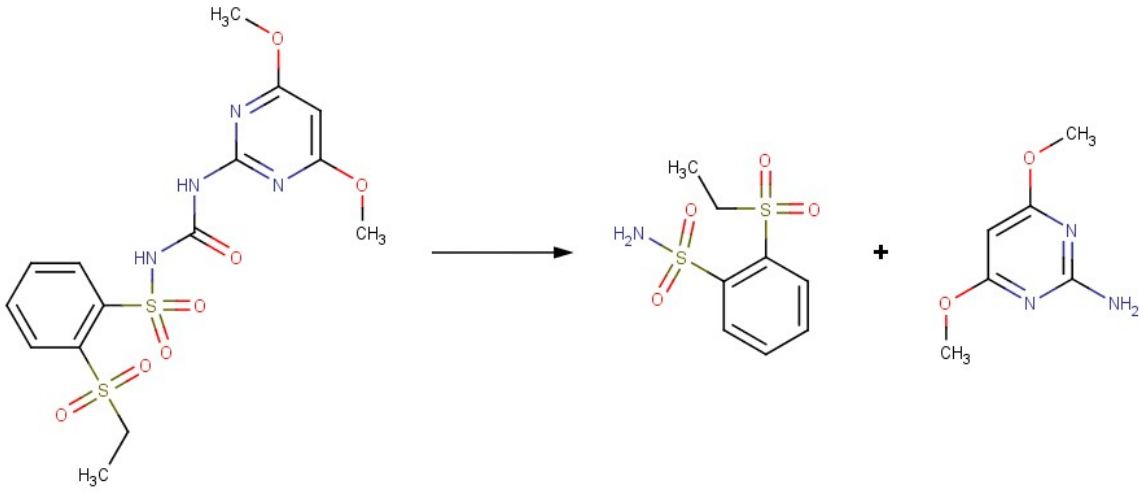
- Halosulfuron-methyl (EFSA, 2011)



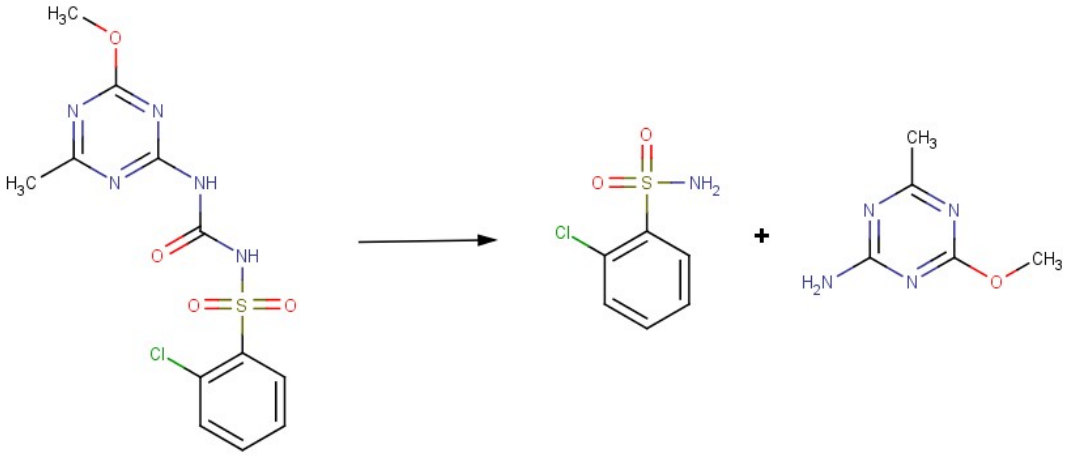
- Triflusulfuron-Methyl (EFSA, 2007a)



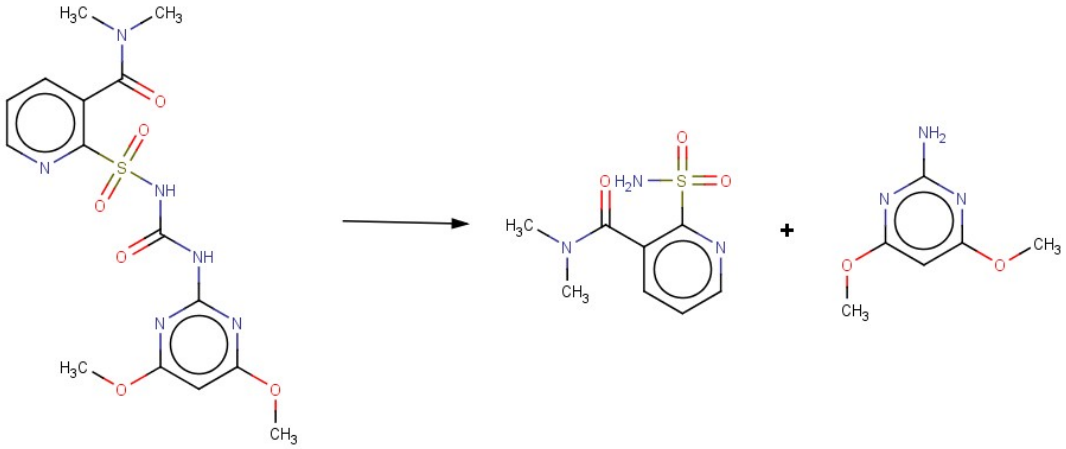
- Rimsulfuron (EFSA, 2005)



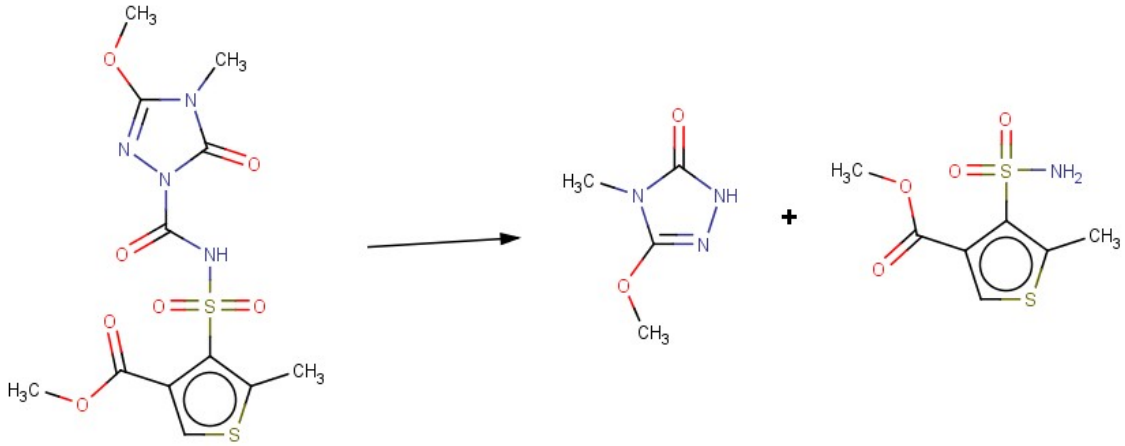
- Chlorsulfuron (EFSA, 2007b)



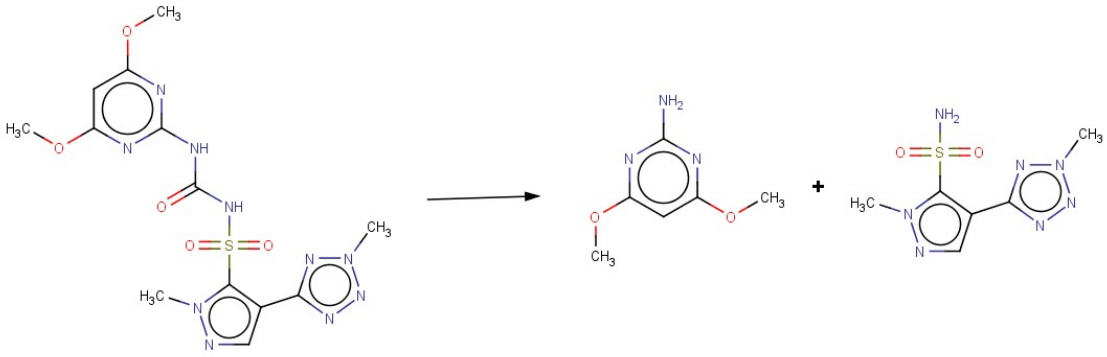
- Nicosulfuron (EFSA, 2006c)



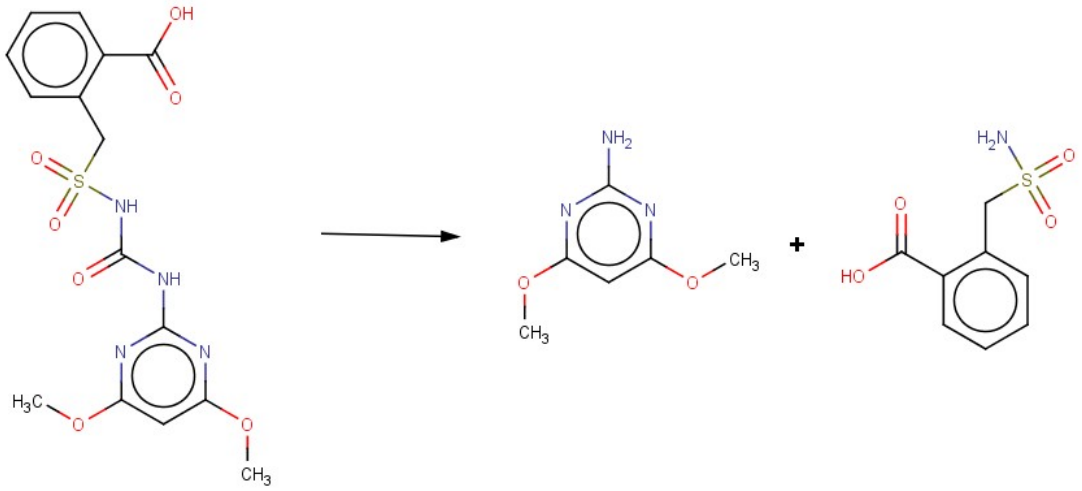
- Thiencarbazone-Methyl (EFSA, 2012).



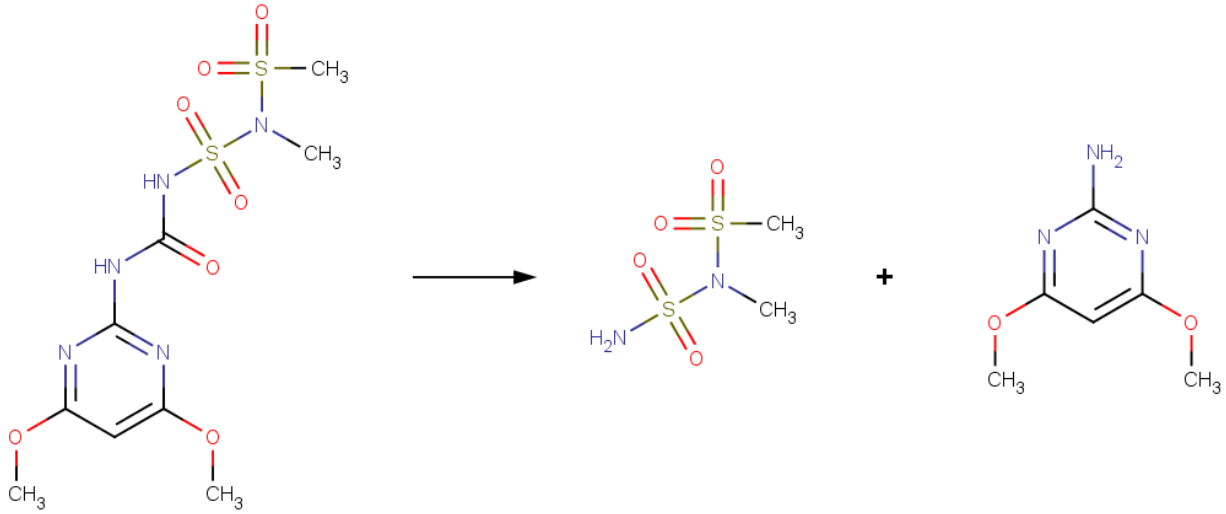
- Azimsulfuron (Boschin *et al*, 2007; EFSA, 2009)



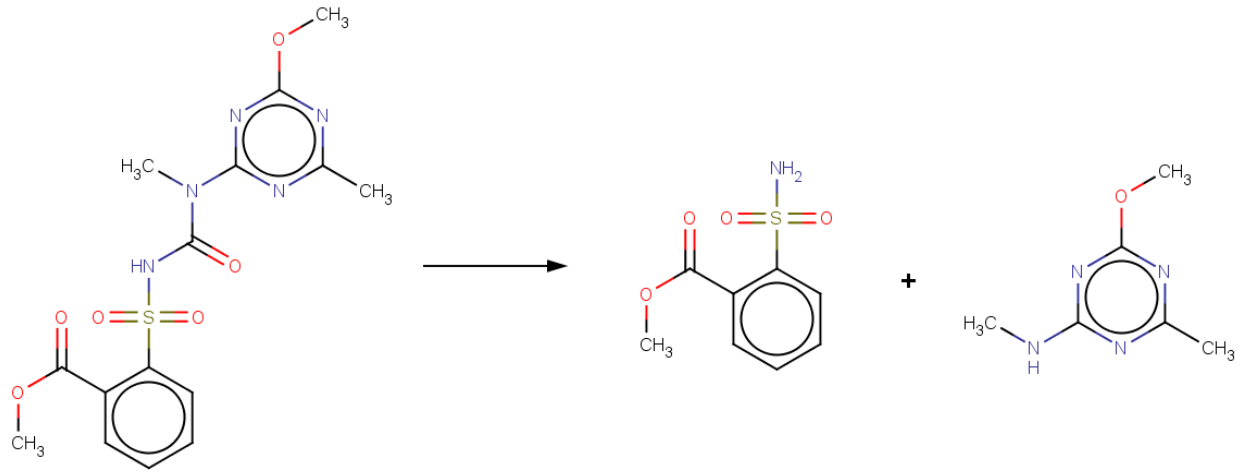
- Bensulfuron Methyl (EFSA, 2006b)



- Amidosulfuran (EFSA, 2006a)



- Tribenuron-methyl (EFSA, 2004)



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Thiocarbamate Hydrolysis

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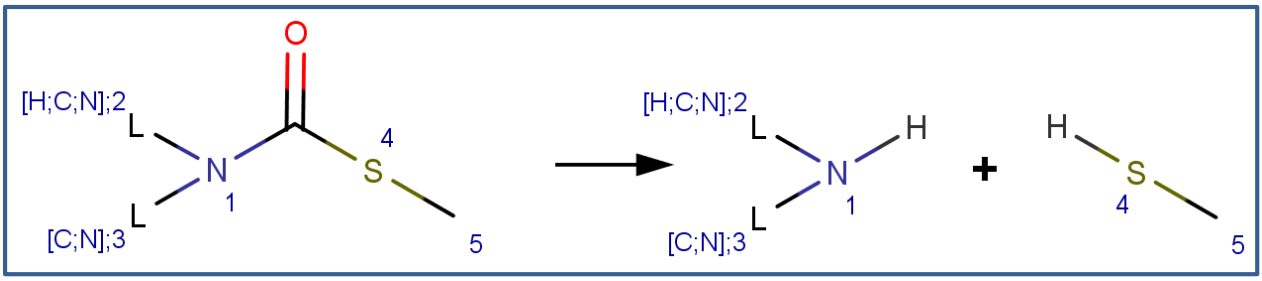

EXAMPLES:

- Diallate (U.S. EPA, 1992, p. 88)

REFERENCES:

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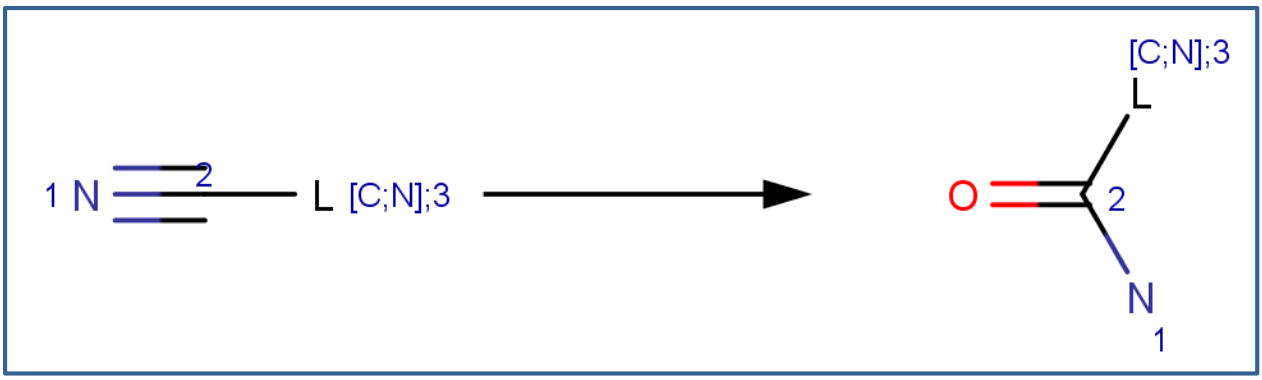
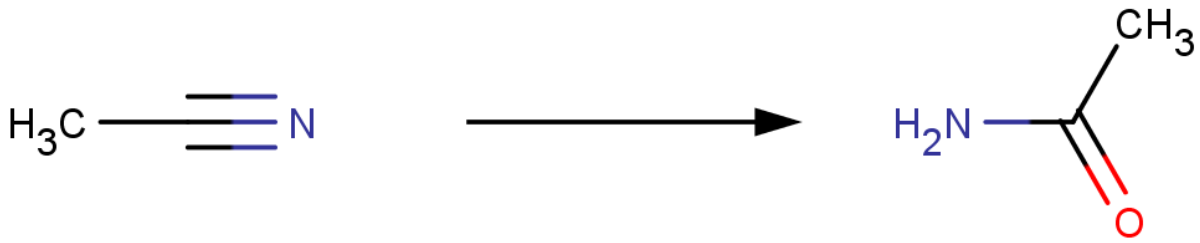
Nitrile Hydrolysis

SCHEME:

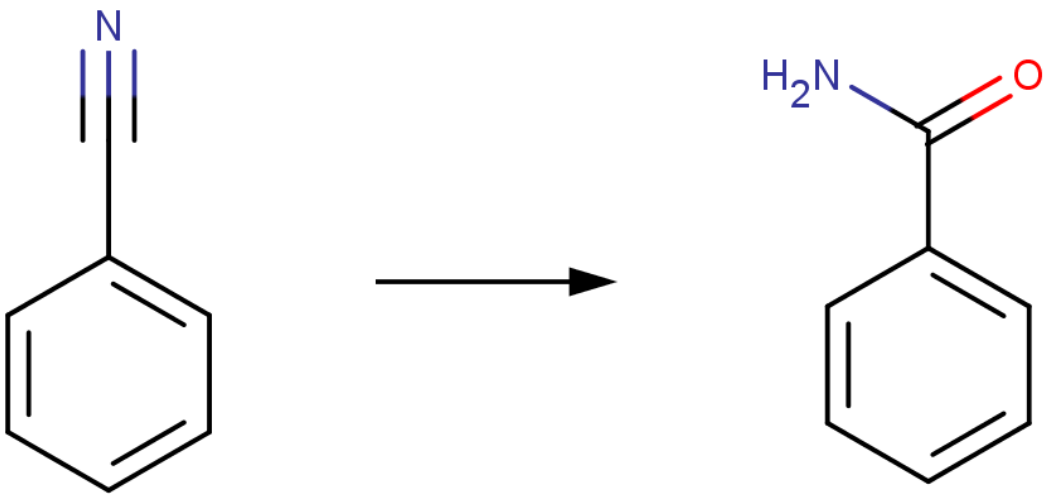


EXAMPLES:

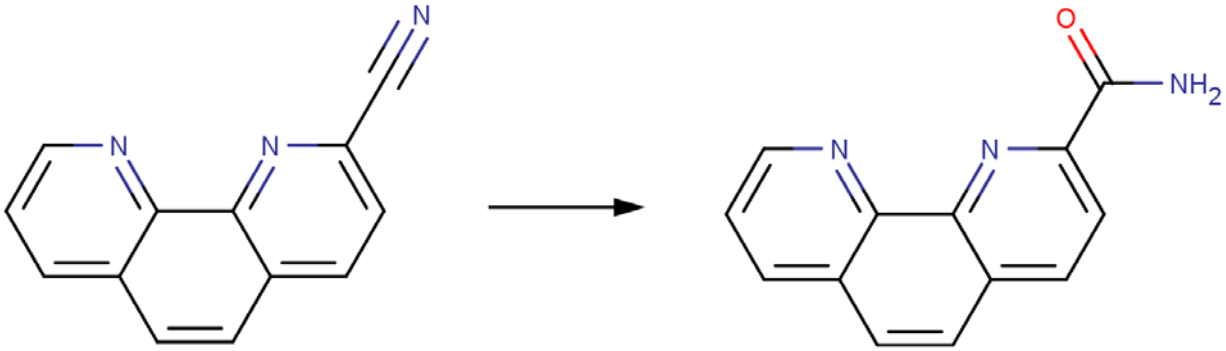
- Acetonitrile (Peskoff and Meyer, 1913; U.S. EPA, 1987)



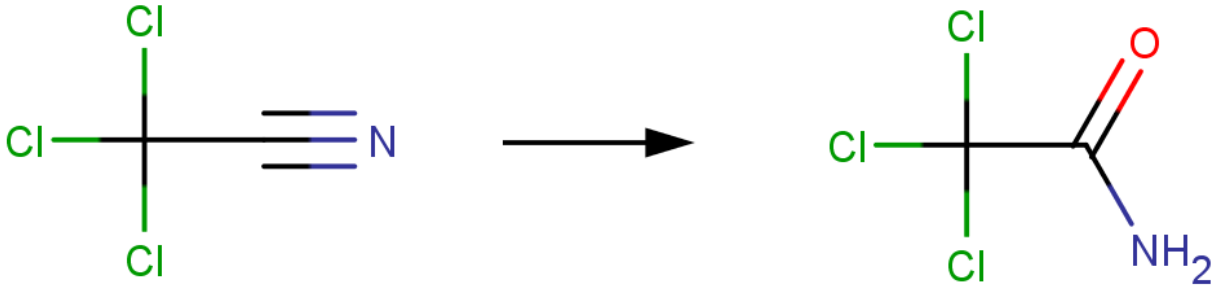
- Benzonitrile (Wiberg, 1955)



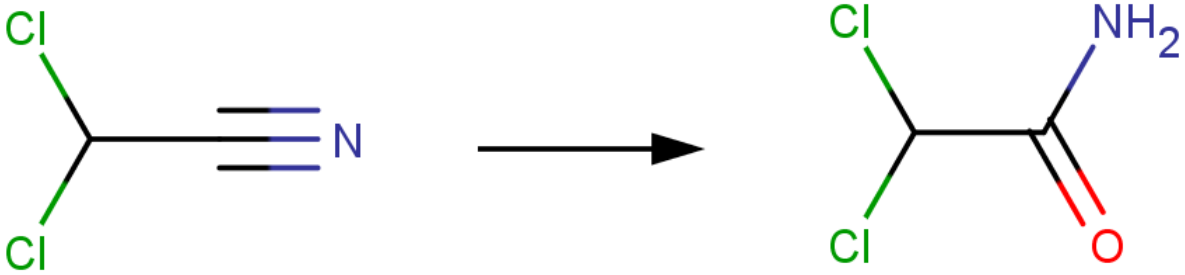
- 1,10-phenanthroline-2-carbonitrile (Breslow *et al*, 1967)



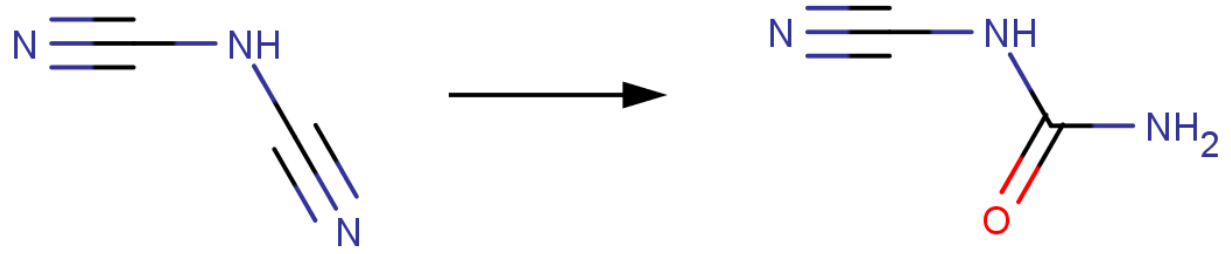
- Trichloroacetonitrile (Glezer *et al*, 1999)



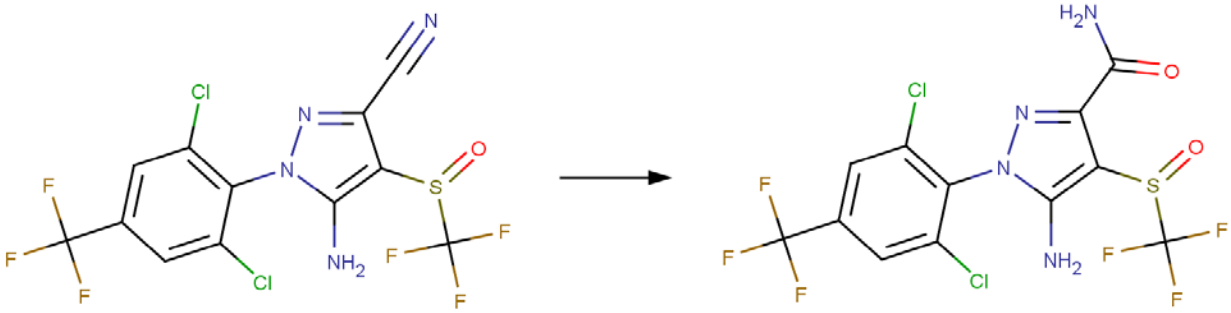
- Dichloroacetonitrile (Reckow *et al*, 2001)



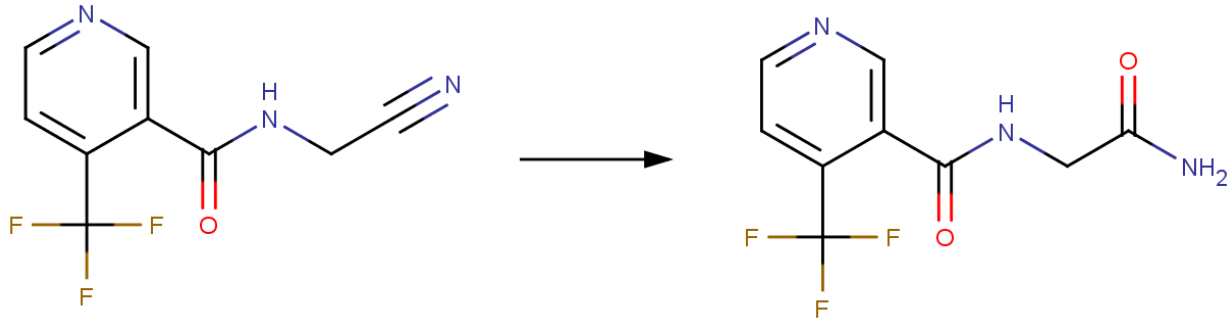
- Dicyanamide (Hill *et al*, 1984)



- Fipronil (EFSA, 2005a)



- Flonicamid (EFSA, 2005b)



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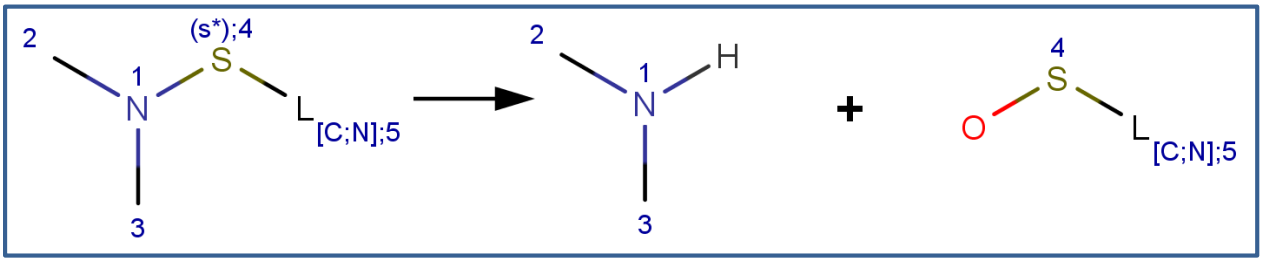
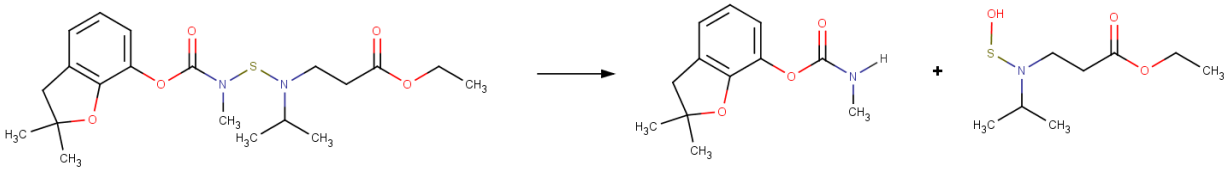
N-S Cleavage

SCHEME:

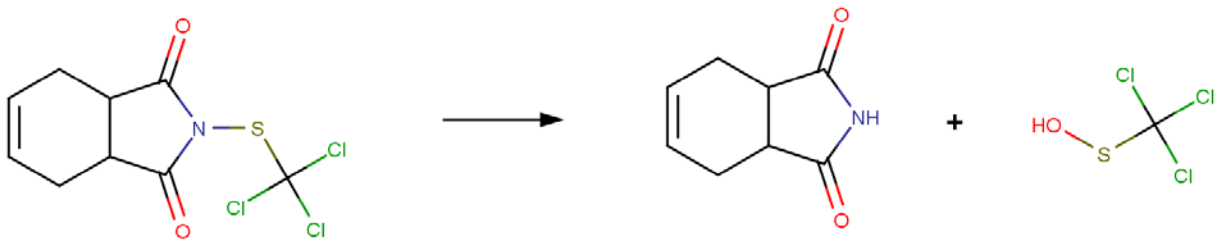


EXAMPLES:

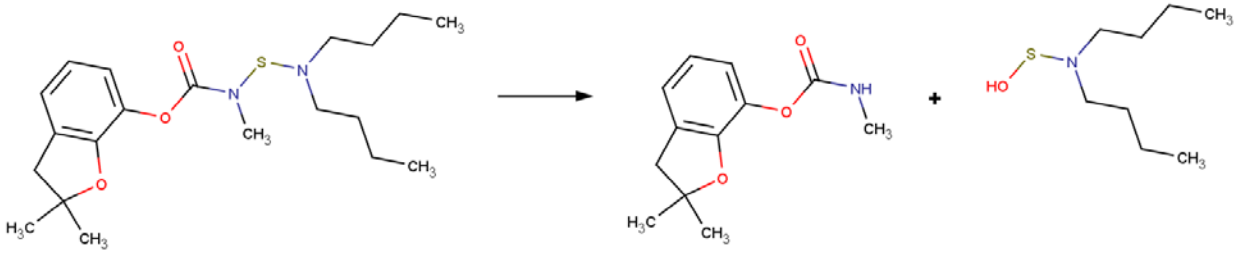
- Benfuracarb (EFSA, 2004a; Iesce *et al*, 2006)



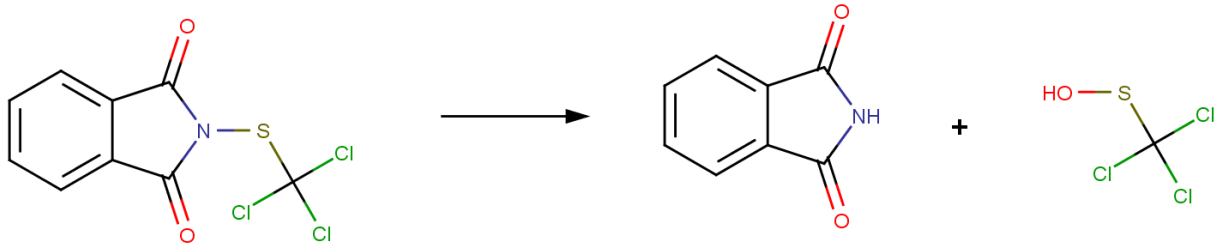
- Captan (EFSA, 2005a; Wolfe et al, 1976)



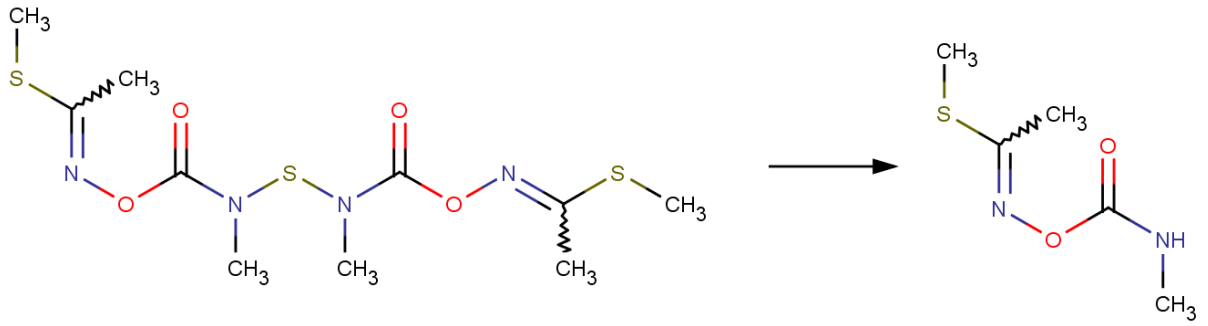
- Carbosulfan (de Melo Plese *et al*, 2005; EFSA, 2004b; Iesce *et al*, 2006; Umetsu *et al*, 1980)



- Folpet (EFSA, 2005b)



- Thiodicarb (EFSA, 2005c)



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List of Scientific/Technical Publications:

- Comparing Metabolite Biotransformation Libraries for Sensitivity and Selectivity toward Mammalian and Microbial Metabolite Formation. M. Card, E. Weber and C. Stevens. Submitted to the Journal of Environmental Science and Technology.

- Development of an Environmental Fate Simulator for New and Proposed Military-Unique Munition Compounds, Caroline Stevens, Kurt Wolfe, Rajbir Parmar, Mike Galvin, Gene Whelan, Said Hilal, Mitch Pelton and Eric Weber. Jannaf Workshop Proceedings – Fate, Transport and Effects of Insensitive Munitions: Issues and Recent Data, Environmental Restoration Report

May 2014

Other Supporting Materials:

User Guide

User Guide for the Chemical Transformation Simulator (CTS) (α-version 1.0)

May 7, 2015

Chemical Transformation Simulator: A Cheminformatics-based Tool for Predicting Transformation Pathways and Physicochemical Properties

The Chemical Transformation Simulator (CTS) User's Guide is designed to provide the first time user a complete understanding of how to use the CTS tool. The User's Guide may be reviewed from start to finish or by moving directly to a topic of interest through selection of the appropriate topic in the Table of Contents.

Table of Contents

Introduction

The Chemical Transformation Simulator (CTS) provides the calculated physico-chemical properties of a target chemical and its transformation products, which are predicted as a function of the reaction system of interest. This is accomplished through the integration of cheminformatics applications for the encoding of process science underlying transformation pathways, computational chemistry tools for the calculation of physico-chemical properties, and software technologies that provide access to on-line databases for environmental descriptors, required for estimating environmental concentrations.

The α-version 1.0 of the CTS consists of 3 modules, the selection and order of execution of which is based on the user's choice of one of three available workflows. The Structure-based Database (SBD) module will also be available in the β-version of the CTS. Two additional modules, the Earth Systems Model (ESM) and Reaction Rate Calculator (RRC), will be functional in the deployable version of the CTS.

α-Version 1.0

- **Chemical Editor (CE):** Provides options for chemical entry, as well as the le speciation of the parent chemical

- **Physicochemical Properties Calculator (PPC):** Calculates p-chem properties for the parent chemical and predicted transformation products based on the executions of multiple p-chem calculators
- **Reaction Pathway Simulator (RPS):** Generates potential transformation products based on user-specified reaction conditions

β-Version

- **Structure-based Database (SBD):** Populated with calculated and measured physico-chemical properties of parent and potential transformation products

Deployable Version

- **Earth Systems Model (ESM):** Provides data mining abilities for environmental descriptors such as pH and temperature
- **Reaction Rate Calculator (RRC):** Calculates transformation products based on the parameterization and execution of QSARs and Algorithms

Background

A key Agency need identified as a high priority in the Chemical Sustainability and Safety (CSS) research program is for high throughput computational systems to simulate environmental fate and transport for a myriad of chemicals for which environmental data are not available. Knowledge of inherent chemical properties (ICP) is essential for the parameterization of environmental fate and transport models. Of the ~85,000 chemicals in the TSCA inventory, it is estimated that high quality measured ICP data are available for less than 2% of these chemicals. Additionally, 20 to 30 new chemicals a month are being assessed through the Office of Pollution Prevention and Toxics (OPPT) Pre-Manufacturing Notification (PMN) process. This ever growing data gap must be addressed through the development of a high throughput computational system for calculating the ICP necessary for the parameterization of environmental fate models used to estimate environmental concentrations of both the parent chemical and predicted transformation products, as a function of environmental conditions.

The key components of the CTS are the development of the physico-chemical properties calculator (PPC) and the Reaction Pathway Simulator (RPS). The PPC is based on a consensus approach that would allow the user to compare output generated by a number of calculators that take different approaches to calculating specific physicochemical properties. The calculators we are currently accessing include (1) SPARC (SPARC Performs Automated Reasoning in Chemistry), which uses a mechanistic-based approach; (2) EPI Suite, which uses a fragment-based approach; (3) TEST (Toxicity Estimation Software Tool), which uses QSAR-based approaches; and (4) ChemAxon plug-in calculators, which use an atom-based fragment approach. The output derived

from these calculators will enable the user to compare the calculated data with measured data in readily accessible web-based databases.

The output of the RPS is based on the selection and execution of reaction libraries that represent one-step reactions for transformation of reactive functional groups (i.e., reduction and hydrolysis). These one-step reactions represent viable transformation pathways based on the identification and subsequent transformation of reactive functional groups. A reaction library for human metabolism for phase 1 transformations, developed by ChemAxon, is also available through the CTS. It is through the development of reaction libraries that allow us to "encode" the known process science, published (current and future) in the peer-reviewed literature. Process science is encoded through the use of Chemical Terms Language and Smart Reaction Smile string, through the cheminformatics applications. The execution of these reaction libraries provides the dominant transformation pathways and products for the chemical of interest as a function of environmental conditions.

Using the CTS Software

Accessing the CTS

The CTS can be accessed through http://134.67.114.1/cts/. Currently, only those users who have access to EPA's intranet have access to the CTS. The home page provides access to the CTS through the selection of one of three CTS workflows and general information concerning the major components of the CTS. The home page also has informational links to the physicochemical calculators, chemical databases and EPA's major environmental regulations controlling chemical use. Links to the information supporting the currently available reaction libraries are also available (see example below for abiotic reduction). Links to structure-searchable databases that are currently under construction will be available in future versions of the CTS.

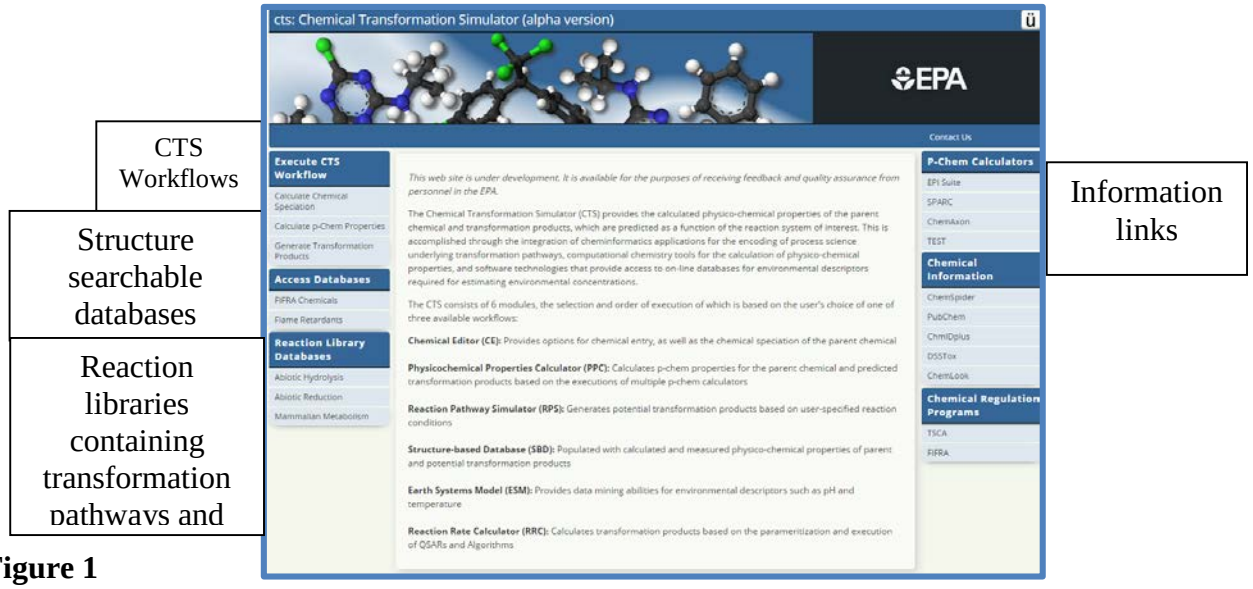


Figure 1

Selection of Abiotic Reduction under the Reaction Library Databases provides the user this screen, which lists the transformation pathways in the abiotic reduction library.

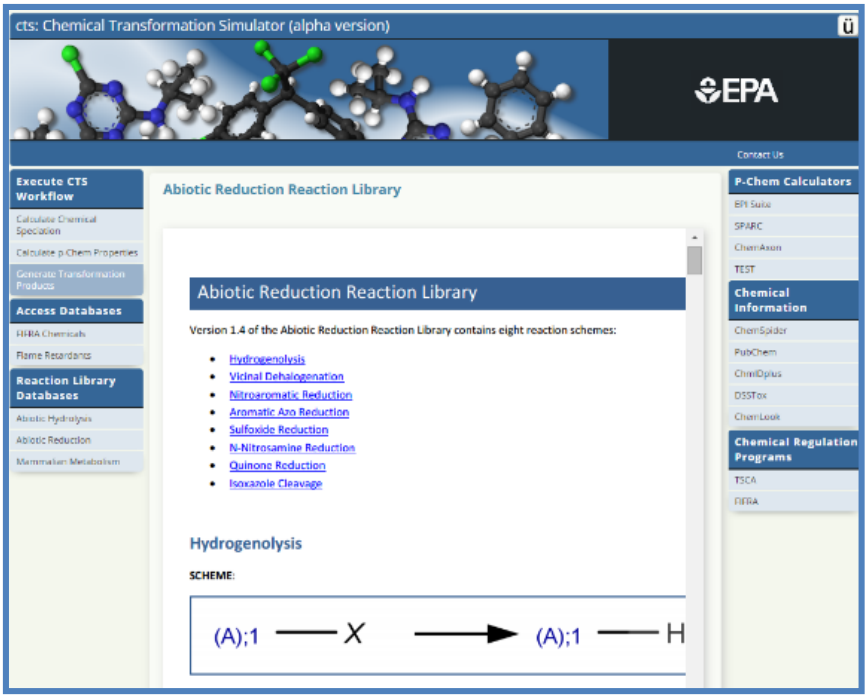


Figure 2

Selecting one of the transformation pathways provides the reaction scheme, and documented examples with references. This example illustrates the information supporting the transformation pathway for Aromatic Azo Reduction.

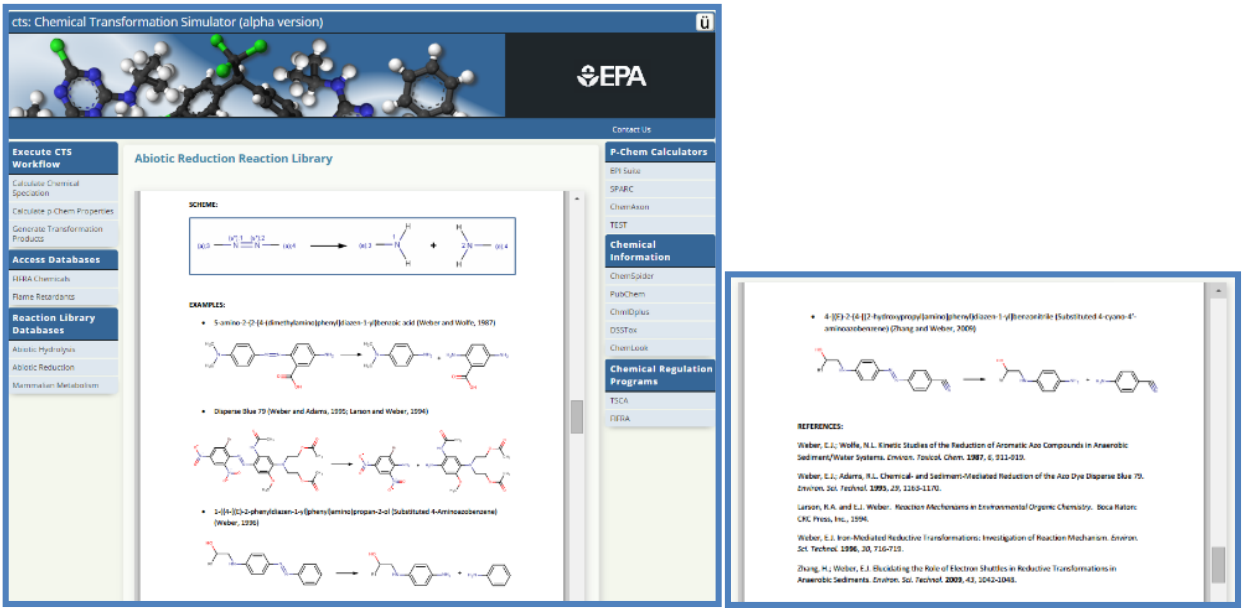


Figure 3

The CTS is executed through the selection of one of three available workflows. Regardless of which workflow is selected, the option is given to enter a single chemical or multiple chemicals.

Single Chemical Entry

For single chemical entry, click the Go to Users Inputs at the bottom of the Workflow Overview page. The Chemical Editor appears where there is the option to either enter a SMILES String, IUPAC chemical name, or CAS# in the Lookup Chemical box, or to draw a chemical structure using the Chemical Editor (see below). Details concerning the use of the chemical editor can be found at https://docs.chemaxon.com/display/marvinsketch/MarvinSketch+User%27s+Guide.

For either case, the user must select the appropriate box after providing the required information. At this point, the Lookup Chemical window will be populated with the SMILES String. The Draw Chemical Structure will display the chemical structure; and the Results window will be populated with the SMILES String, IUPAC name, formula, and molecular weight of the chemical of interest.

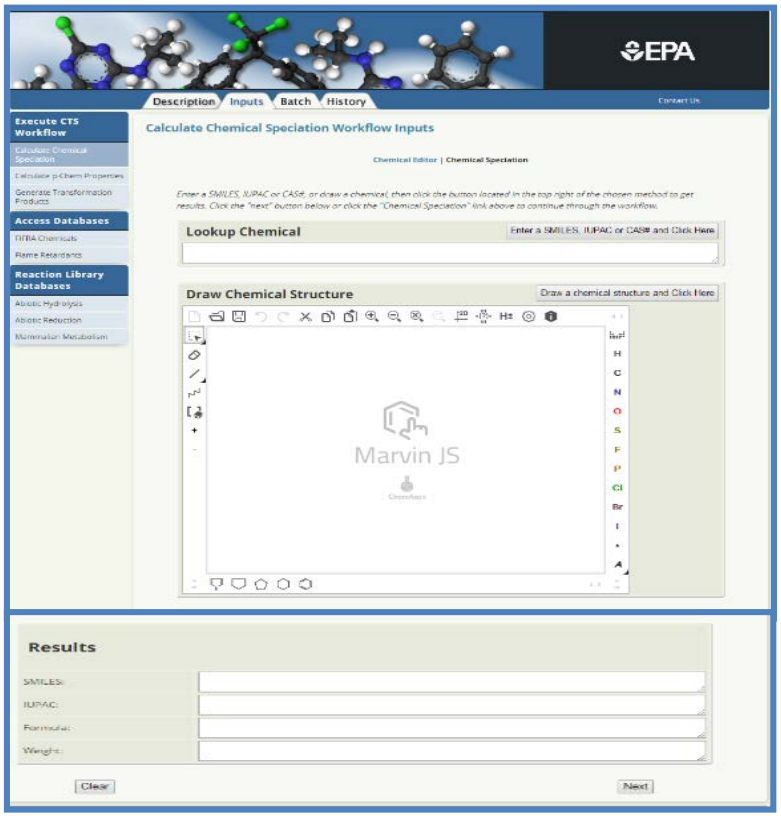


Figure 4

Multiple Chemical Entry

For Multiple Chemical Entry, the user selects the Batch Tab that is located at the top of the page. The Batch Tab is currently under construction and will be available in an updated version of the CTS. The required format for the text file is shown below:

```
CC1(C)[C@@H](\C=C(/Cl)C(F)(F)F)[C@H]1C(=O)O[C@H](C#N)c1cccc(Oc2ccccc2)c1
Br/C(Br)=C/[C@H]3[C@@H](C(=O)O[C@H](C#N)c2cccc(Oc1ccccc1)c2)C3(C)C
C1CN(C(=N1)N[N+](=O)[O-])CC2=CN=C(C=C2)Cl
CN\C(NCC1CCOC1)=N/[N+]([O-])=O
CC(=O)O[C@H]1CCC2[C@@]1(C=CC3=C4CCC(=O)C=C4CCC23)C
C[C@]12CC[C@H]3[C@@H](CCC4=CC(=O)CC[C@]34C)[C@@H]1CC[C@@H]2O
CCS(=O)(=O)c1nc2ccccn2c1S(=O)(=O)NC(=O)Nc1nc(OC)cc(OC)n1
COC(=O)c1ccccc1S(=O)(=O)NC(=O)N(C)c1nc(C)nc(OC)n1
CCOC(=O)CC(C(=O)OCC)SP(=S)(OC)OC
CCOP(=S)(OCC)Oc1c(cc(c(n1)Cl)Cl)Cl
```

For the SPARC vapor pressure and water solubility calculators, melting points are also required using the format shown below:

```
CC1(C)[C@@H](\C=C(/Cl)C(F)(F)F)[C@H]1C(=O)O[C@H](C#N)c1cccc(Oc2ccccc2)c1 ! 49.2
Br/C(Br)=C/[C@H]3[C@@H](C(=O)O[C@H](C#N)c2cccc(Oc1ccccc1)c2)C3(C)C ! 100.35
C1CN(C(=N1)N[N+](=O)[O-])CC2=CN=C(C=C2)Cl ! 160.73
CN\C(NCC1CCOC1)=N/[N+]([O-])=O ! 116.49
CC(=O)O[C@H]1CCC2[C@@]1(C=CC3=C4CCC(=O)C=C4CCC23)C ! 155.71
C[C@]12CC[C@H]3[C@@H](CCC4=CC(=O)CC[C@]34C)[C@@H]1CC[C@@H]2O ! 155.85
CCS(=O)(=O)c1nc2ccccn2c1S(=O)(=O)NC(=O)Nc1nc(OC)cc(OC)n1 ! 201.4
COC(=O)c1ccccc1S(=O)(=O)NC(=O)N(C)c1nc(C)nc(OC)n1 ! 141
CCOC(=O)CC(C(=O)OCC)SP(=S)(OC)OC ! 2.8
CCOP(=S)(OCC)Oc1c(cc(c(n1)Cl)Cl)Cl ! 42.1
```

Reporting Options

With release of the β-version of the CTS, the user will have three options for reporting the results of the CTS output:

- pdf and html files providing the output of the individual workflows (available in the α-version of the CTS)
- Excel file providing the p-chem properties for the parent chemical and generated transformation products (available in the β-version of the CTS)
- Structure-searchable database providing the p-chem properties for the parent chemical and generated transformation products (available in the β-version of the CTS)

The .pdf and .html buttons appear on the right of the results page, regardless of the workflow. Clicking on the .pdf button generates the pdf file that is available for viewing at the bottom left side of the results window (see p. 12 for an example).

Execution of the CTS Workflows

The user executes the CTS through the selection of one of three available workflows:

- Calculate Chemical Speciation
- Calculate p-Chem Properties
- Generate Transformation Products

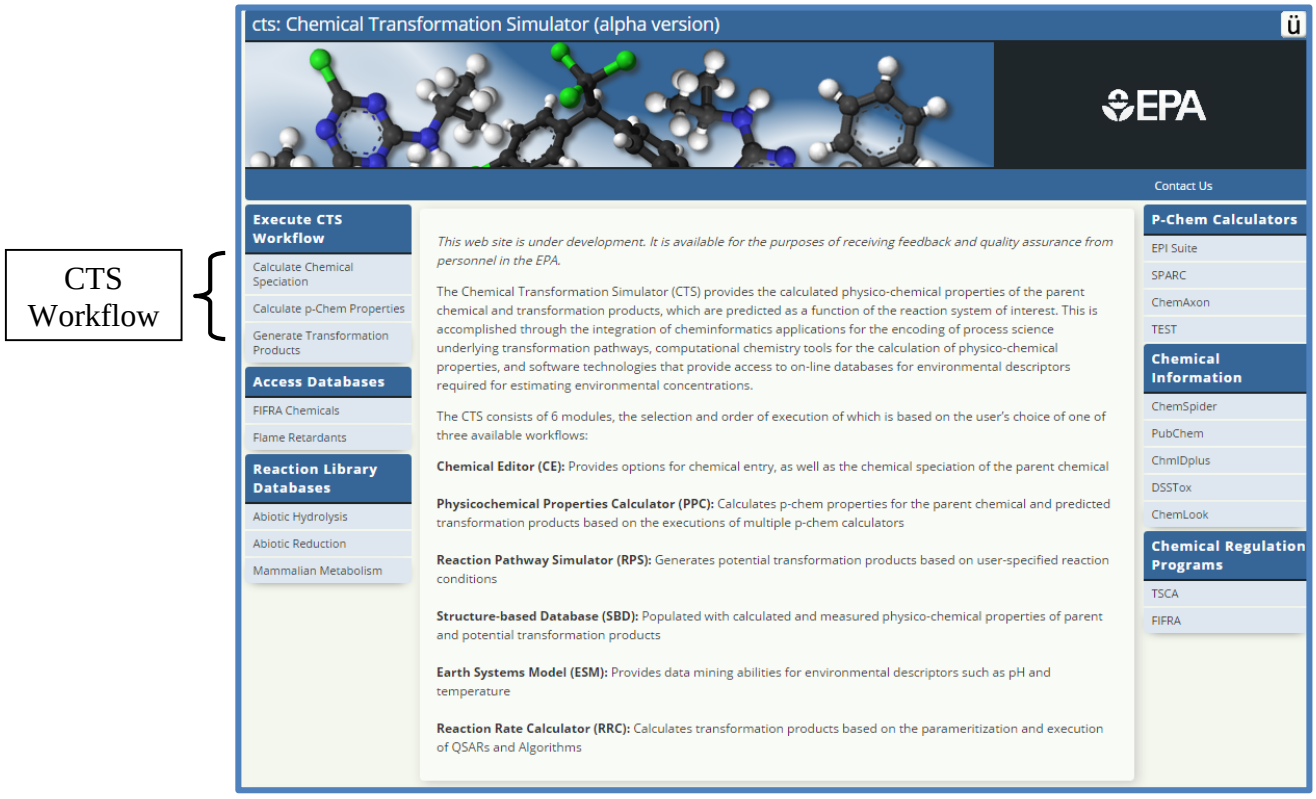


Figure 5

‘

Calculate Chemical Speciation Workflow

Selection of the Calculate Chemical Speciation Workflow provides this page illustrating the workflow overview. Click on the Go to User Inputs button to provide the chemical(s) of interest.

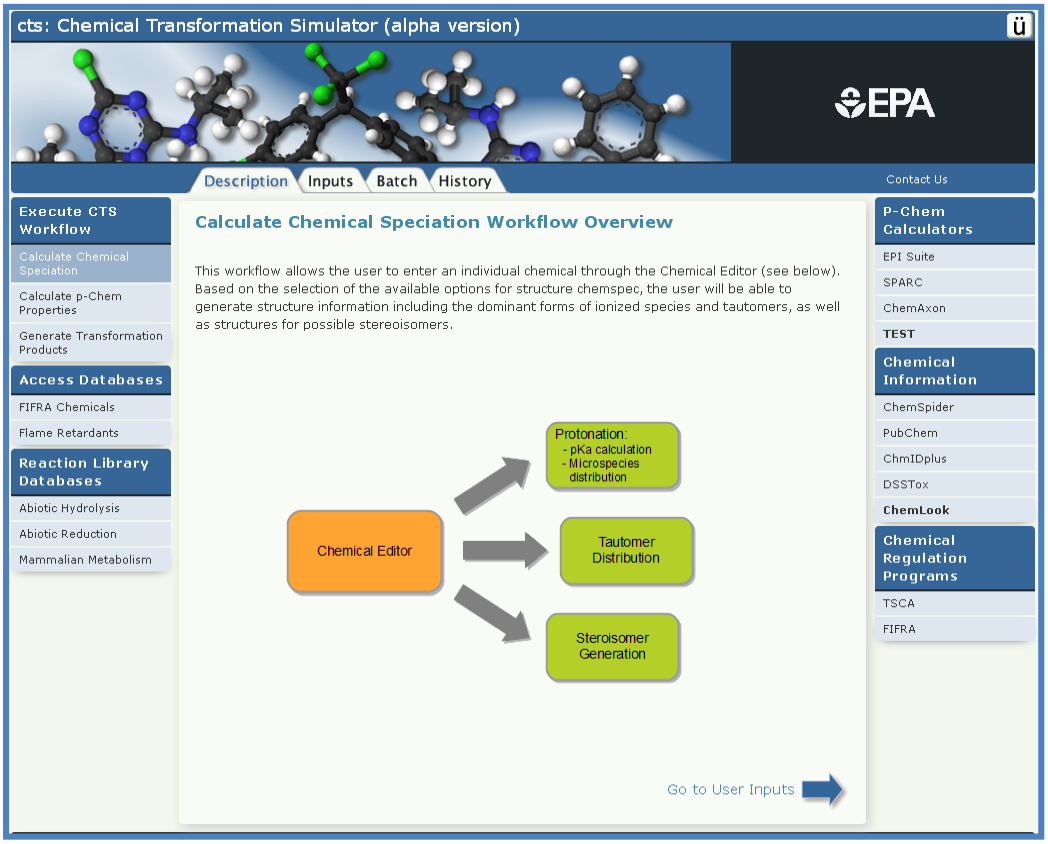


Figure 6

Clicking on the Go to User Inputs button, the user is taken to the Chemical Editor, the use of which is described on p. 6. For the following example, 4-aminophenol was entered into the Chemical Editor.

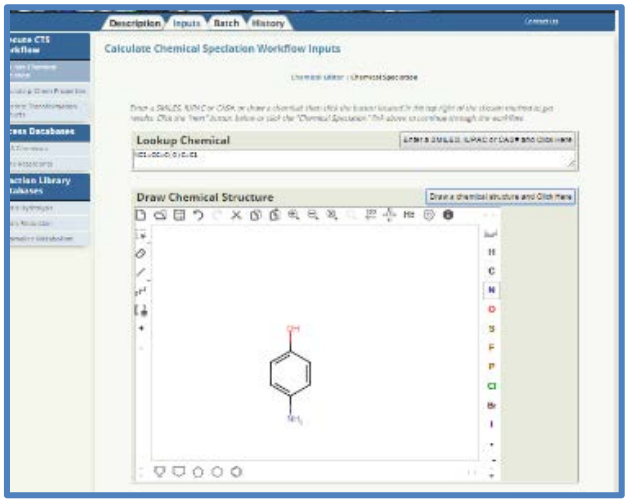


Figure 7

After selection of the Next button at the bottom of the Chemical Editor, this screen provides the user with the option to select amongst three available options for calculating chemical speciation:

- Calculate Ionization Constants
- Calculate Dominant Tautomer Distribution
- Calculate Stereoisomers

The user can select any combination of the calculators. The user has the option to use the provided default values or to change them to values required by the user. The following parameters can be adjusted as needed:

- Calculate Ionization Constants
  - Number of decimals: Number of decimal places calculated for acidic and basic pK_a values
  - pH Lower limit: Specifies the lower end of the pH range for which the microspecies will be generated
  - pH Upper limit: Specifies the upper end of the pH range for which the microspecies will be generated
  - Generate Major Microspecies at pH: Generates the Major Microspecies at the specified pH
  - pH step size: Specifies the pH step size for the X-Axis of the plot illustrating the distribution of the microspecies as a function of pH
- Calculate Dominant Tautomer Distribution
  - Maximum Number of Structures: Specifies the maximum number of structures that will be generated.
  - At pH: Specifies the pH at which the dominant tautomer distribution will be calculated
- Calculate Stereoisomers
  - Maximum Number of Structures: Specifies the maximum number of structures that will be generated.

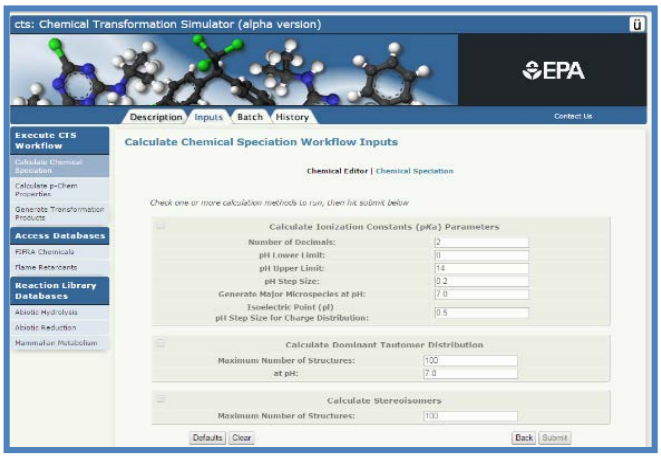


Figure 8

Calculate Ionization Constants

Once the calculator(s) has been chosen and the appropriate parameters entered, the user selects the submit key to view the results. The calculator for ionization constants has been chosen for the purpose of this demonstration.

Figure 8

The results of the ionization constant calculation are illustrated in the window below:

User Inputs: The molecular information and ionization parameters provided by the user.

- **pKa Calculations:** Provides the user with the chemical structure entered by the user, the generated microspecies, and the distribution of microspecies as a function of pH over the pH range specified by the user. These results are color coded.
- **Isoelectric Point:** The isoelectric point is provided as well as a graph illustrating the charge on the chemical as a function of pH.
- **Major Microspecies:** The dominant microspecies formed at the pH selected by the user.

The .pdf and .html buttons appear on the right of the results page, regardless of the workflow. Clicking on the .pdf button generates the pdf file that is available for viewing at the bottom right side of the results window.

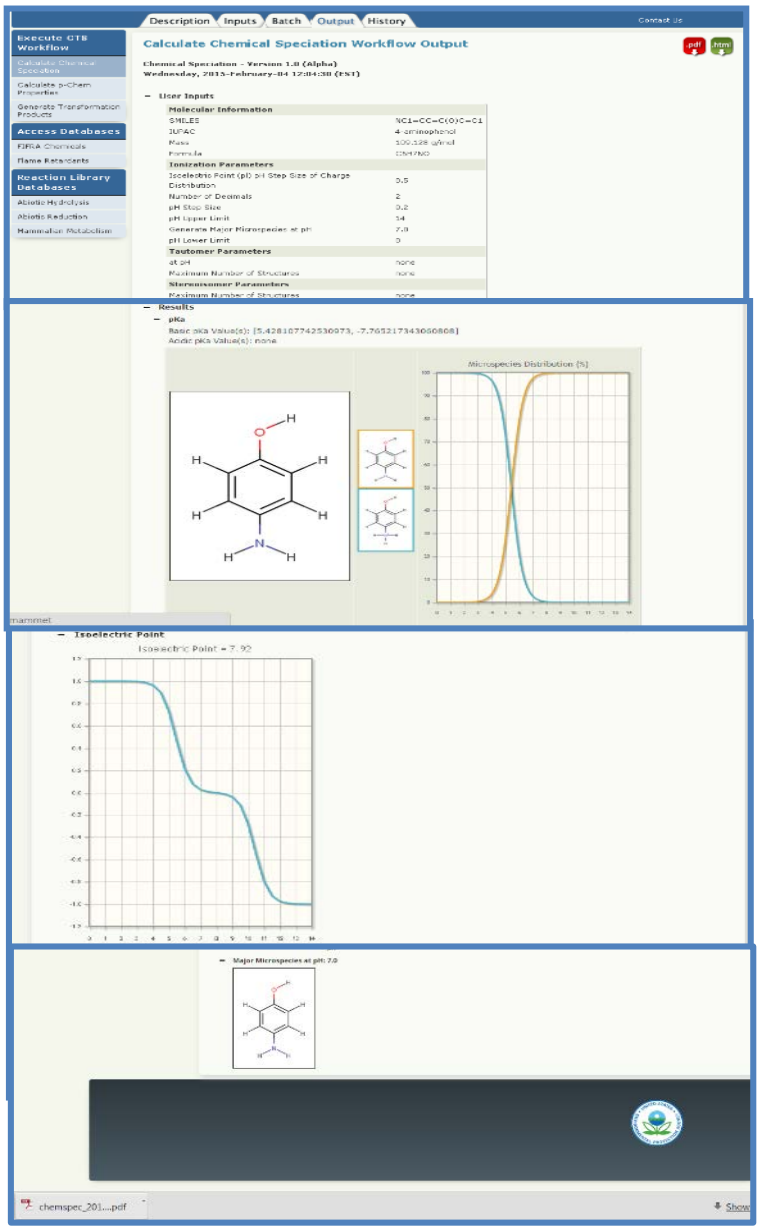

Description
Inputs
Batch
Output
History
Calculate Chemical Speciation Workflow Output
Chemical Speciation - Version 1.0 (Alpha)
Wednesday, 2015-February-04 12:04:38 (EST)
User Inputs
Molecular Information
SMILES
NC1=CC=C(O)C=C1
IUPAC
4-aminophenol
Ionization Parameters
Tautomer Parameters
Results
pKa
Basic pKa Value(s): [5.428107742530973, -7.765217343060808]
Acidic pKa Value(s): none
Microspecies Distribution (%)
Isoelectric Point
Isoelectric Point = 7.92
Major Microspecies at pH: 7.0

Figure 9

Calculate Dominant Tautomer Distribution

For the purpose of this demonstration, 1-phenylbutane-1,3-dione has been entered into the Chemical Editor.

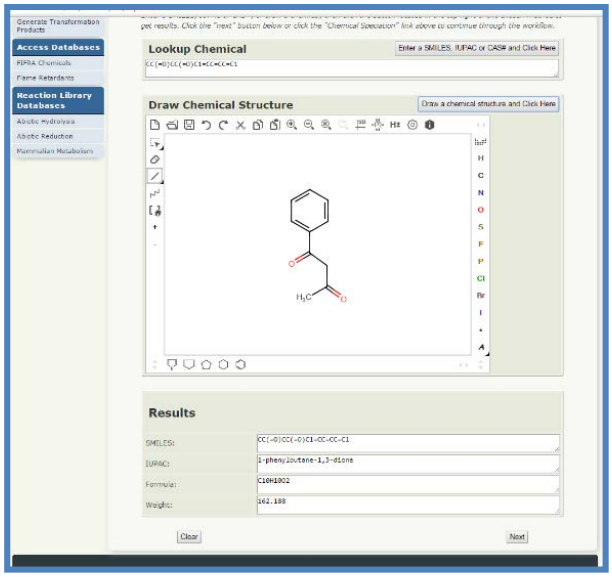


Figure 10

Clicking on the Next button takes the user to the Calculate Chemical Speciation Workflow Inputs page. After selecting the Calculate Dominant Tautomer Distribution option, the user can enter a limit for the number of possible tautomers and the pH value for which the distribution will be calculated. The default values are pH 7.4 and a limit of 100 tautomers.

Figure 11

The Output screen shows the User Inputs as well as the tautomer distribution for the chemical of interest. The individual structures can be enlarged by placing the cursor on top of the structure. The molecular information including the formula, IUPAC name, mass and SMILES string is also provided.

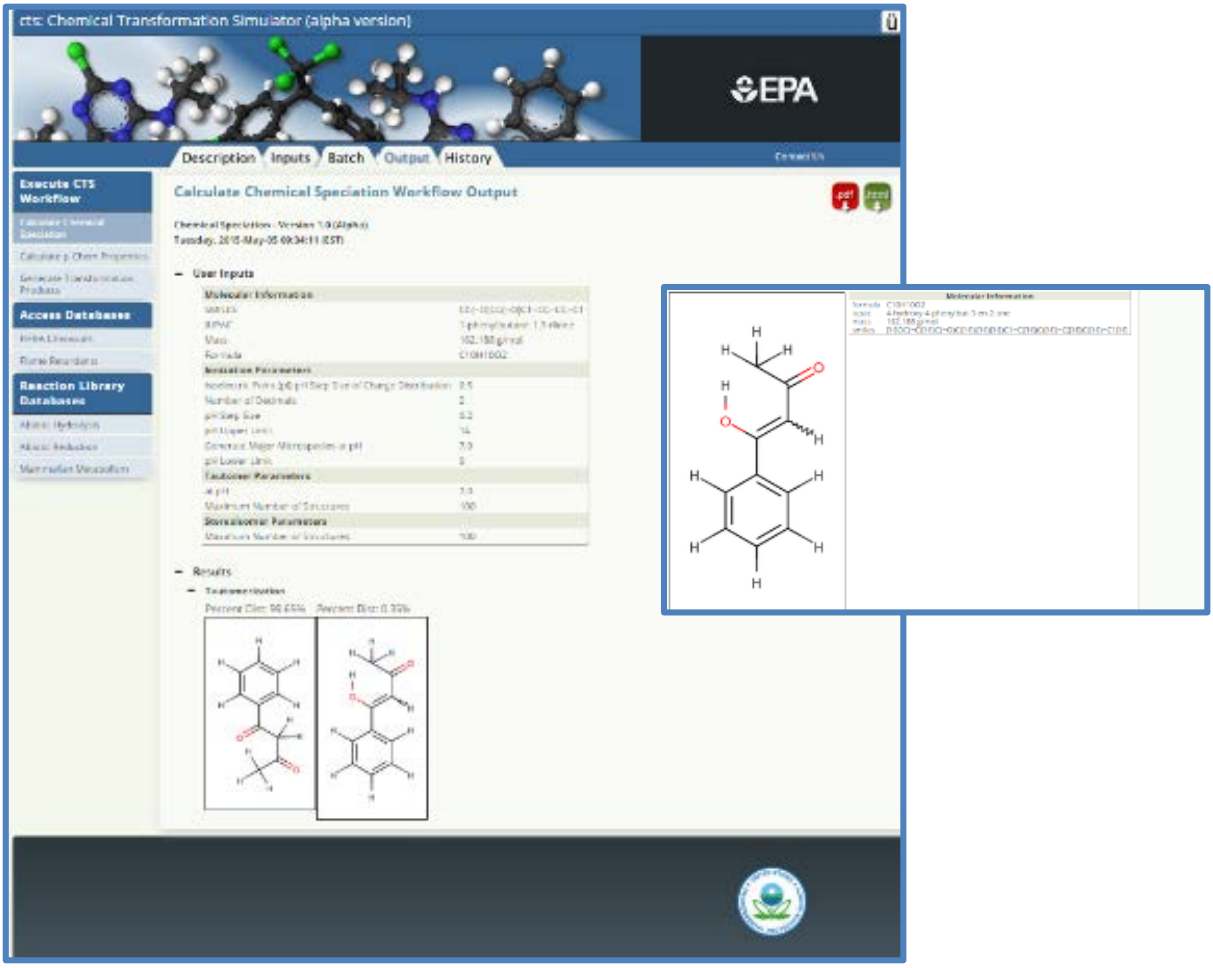


Figure 12

Calculate Stereoisomers

For the purpose of this demonstration, 1,2,3,4,5,6-hexabromocyclohexane has been entered into the Chemical Editor.

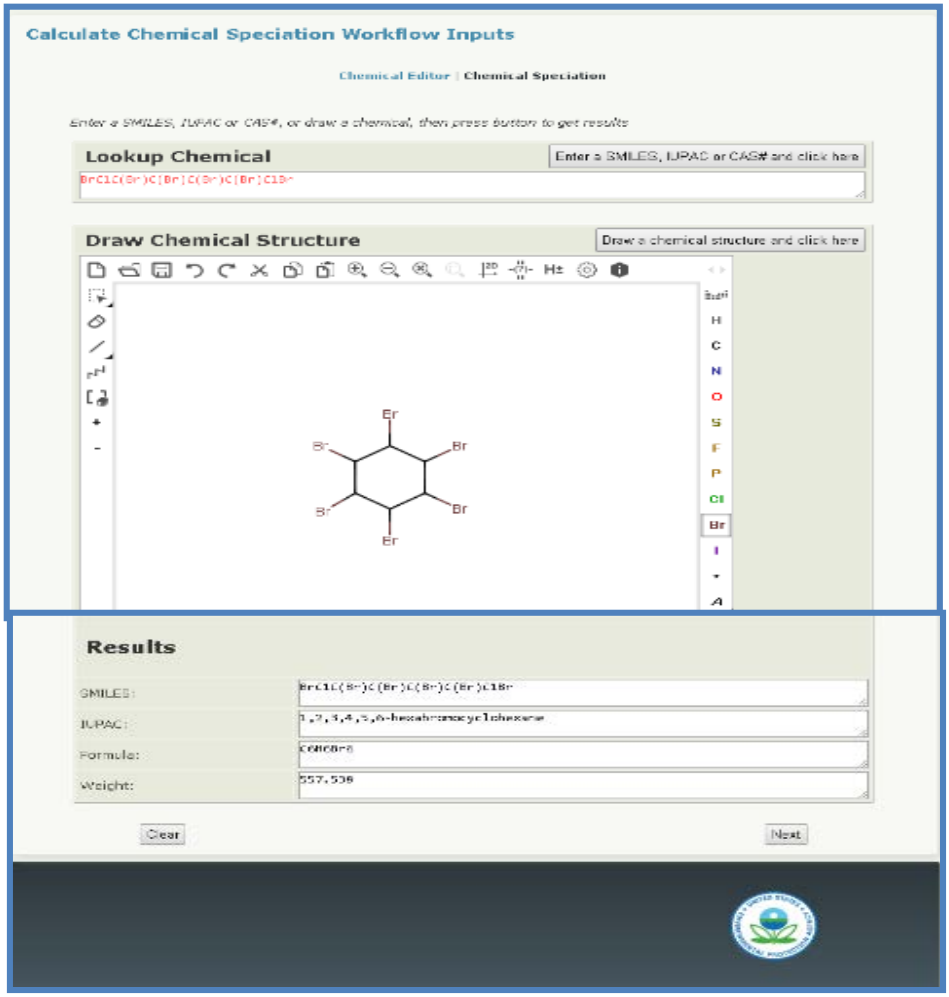


Figure 13

After selecting the Calculate Stereoisomers option, the user can enter a limit for the maximum number of possible stereoisomers. The default value is 100 stereoisomers.

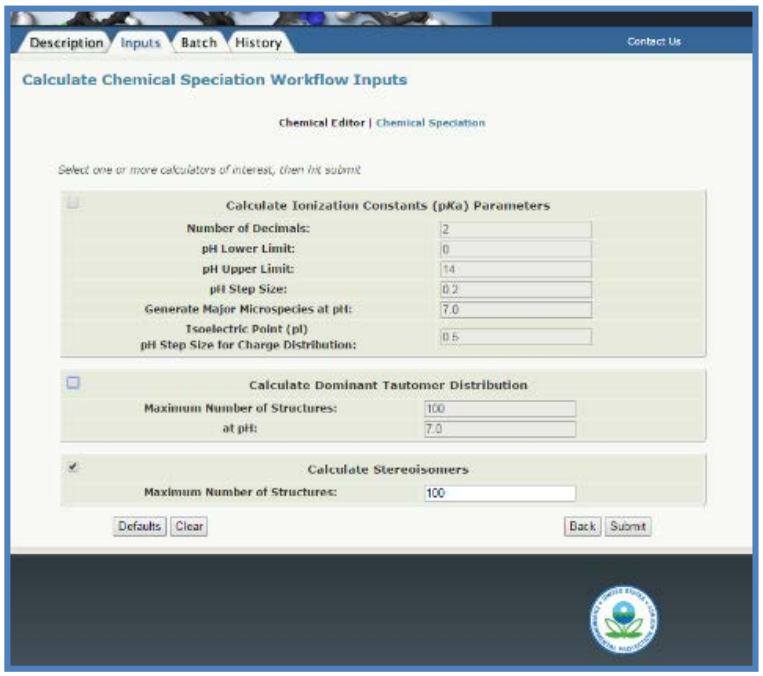
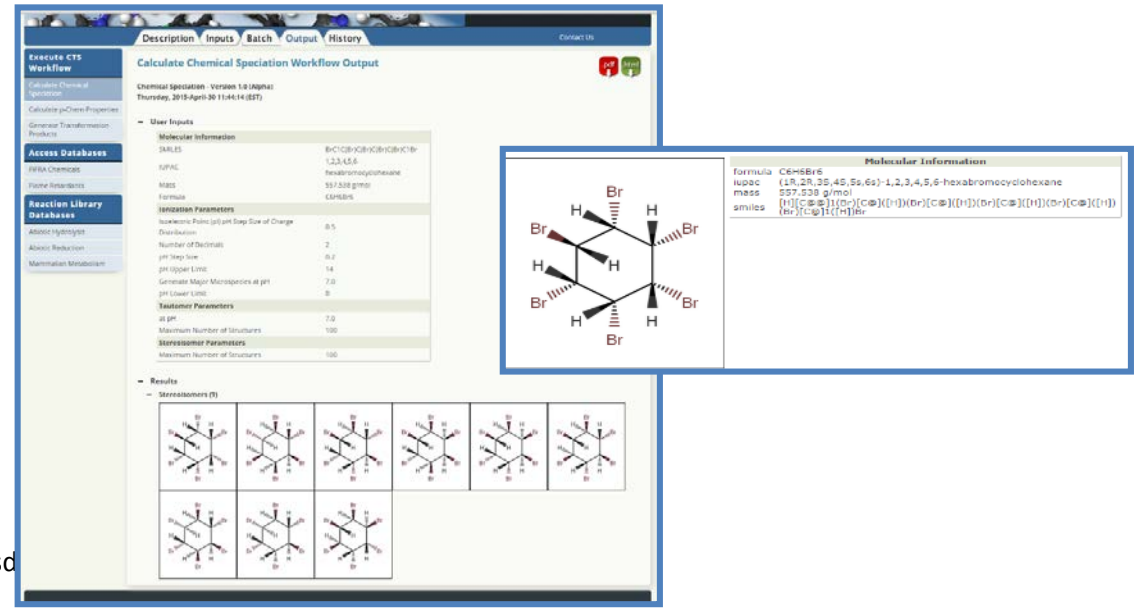


Figure 13

Clicking on the Next button provides the results of the calculation, which illustrate that 1,2,3,4,5,6-hexabromocyclohexane can exist as nine different isomers. The individual structures can be enlarged by placing the cursor over the structure. The molecular information including the formula, IUPAC name, mass and SMILES string is also provided.



sdfasd

Figure 13

Calculate p-Chem Properties Workflow

Selection of the Calculate p-Chem Properties Workflow provides this page illustrating the workflow overview. Click on the Go to User Inputs to provide the chemical(s) of interest.

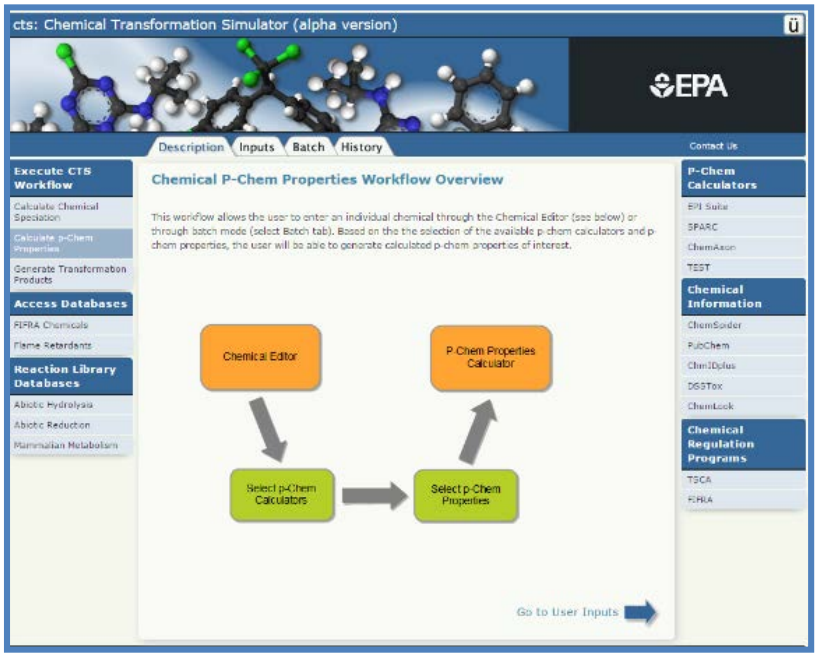


Figure 14

For the purpose of this demonstration, 1-methoxybenzene-2,4-dinitrobenzene has been entered into the chemical editor. The user selects the Next button to choose the p-chem calculators and p-chem properties of interest.

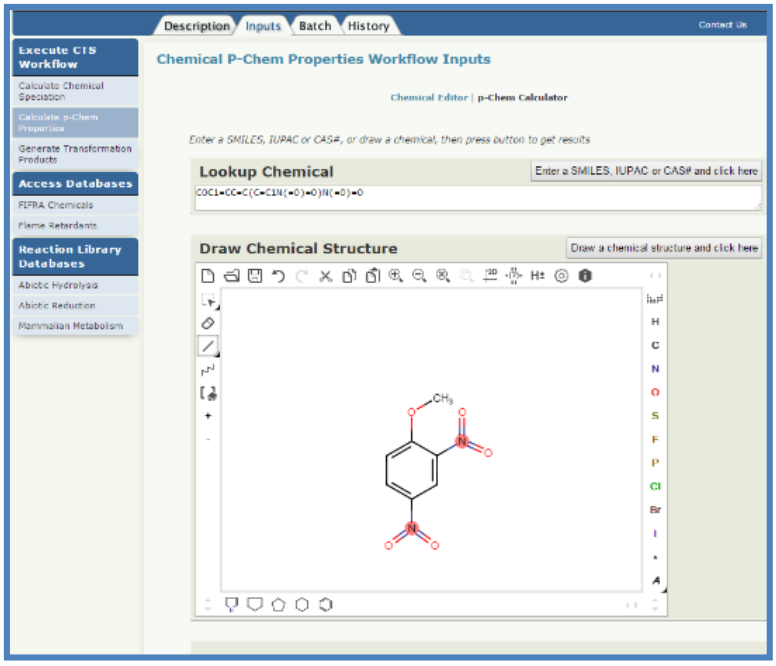


Figure 15

The Chemical p-Chem Properties Workflow Inputs screen provides the user with the options to select p-chem properties and the p-chem calculators of interest. Selection of the All button for the p-chem properties will only provide the available properties for the selected p-chem calculators.

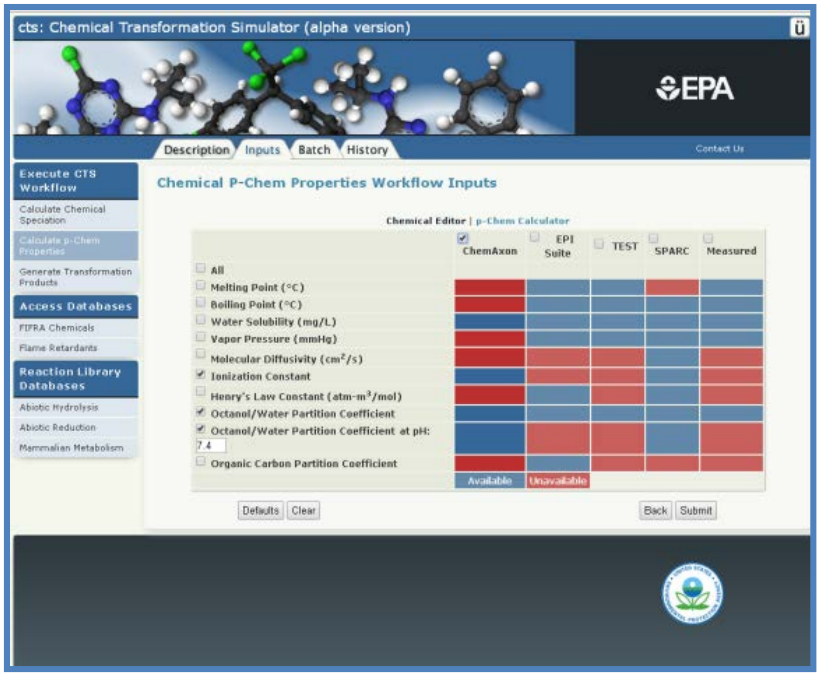


Figure 16

The Calculate p-Chem Properties Workflow Outputs screen provides the user with the results of the previously selected p-chem properties.

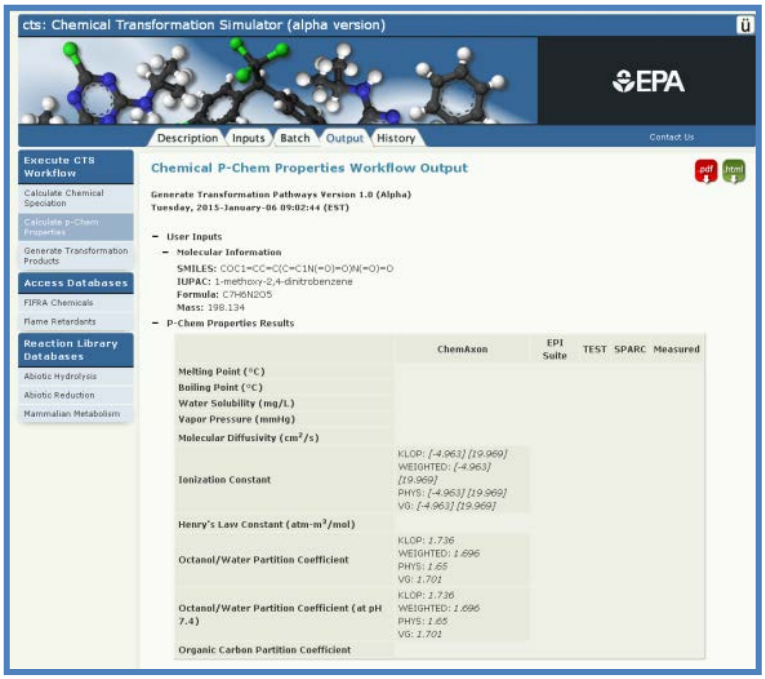


Figure 16

Generate Transformation Products Workflow

Selection of the Generate Transformation Products Workflow provides this window illustrating the workflow overview. Click on the Go to User Inputs button to provide the chemical(s) of interest.

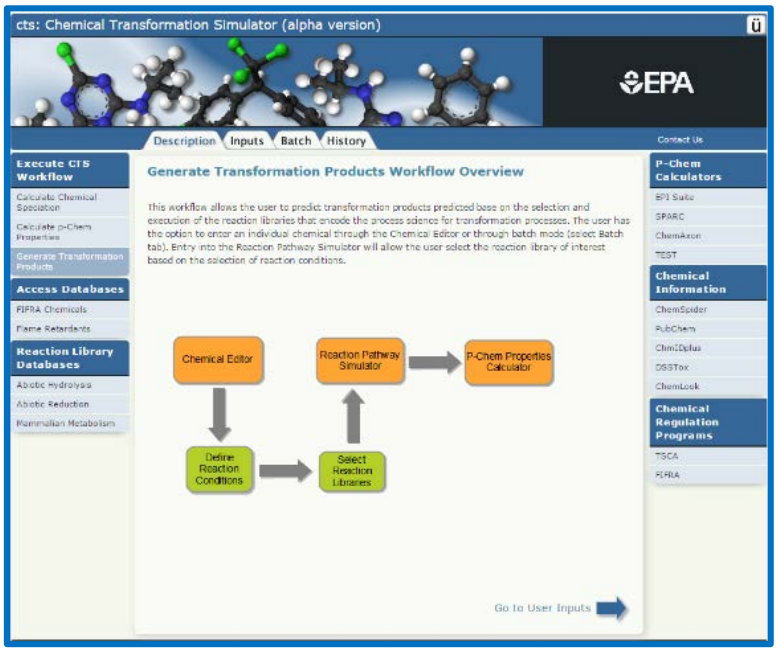


Figure 17

For the purpose of this demonstration, hexachloroethane has been entered into the chemical editor.

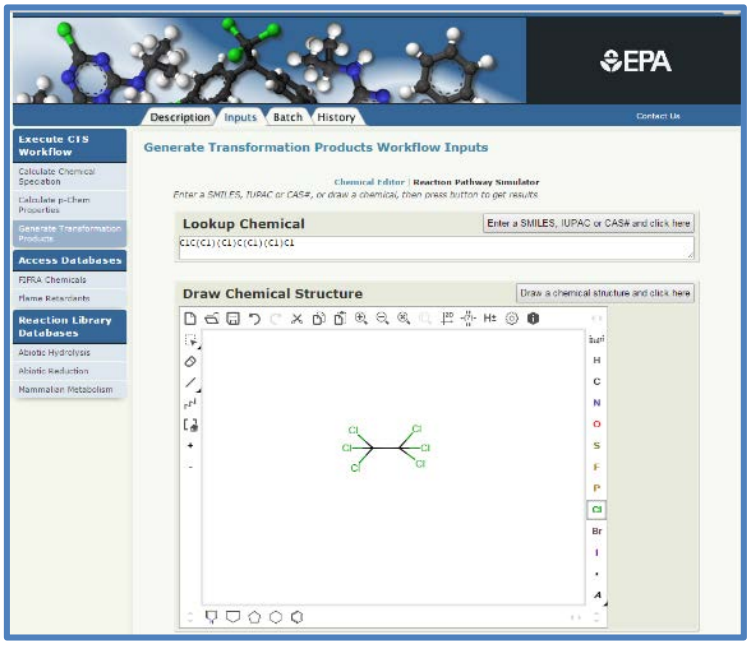


Figure 18

The first required input is the selection of the reaction libraries based on the transformation pathways of interest. Three reaction libraries, including abiotic hydrolysis, abiotic reduction and

Phase 1 mammalian metabolism, are available in the α-version of the CTS. The user is given 3 options for the selection of the libraries based on:

- Reaction System Conditions
- OCSPP Harmonized Test Guidelines
- User Selected (Advanced)

Figure 19

Selection of the Reaction System Conditions provides the user with 2 options for reaction systems: Environmental or Mammalian.

Selection of the Environmental Reaction System provides the user with the option to select respiration type: Aerobic or Anaerobic.

Selection of anaerobic respiration opens the window with the reactions libraries for the transformation pathways that are currently available and will potentially occur under these reaction conditions, which includes abiotic hydrolysis and abiotic reduction.

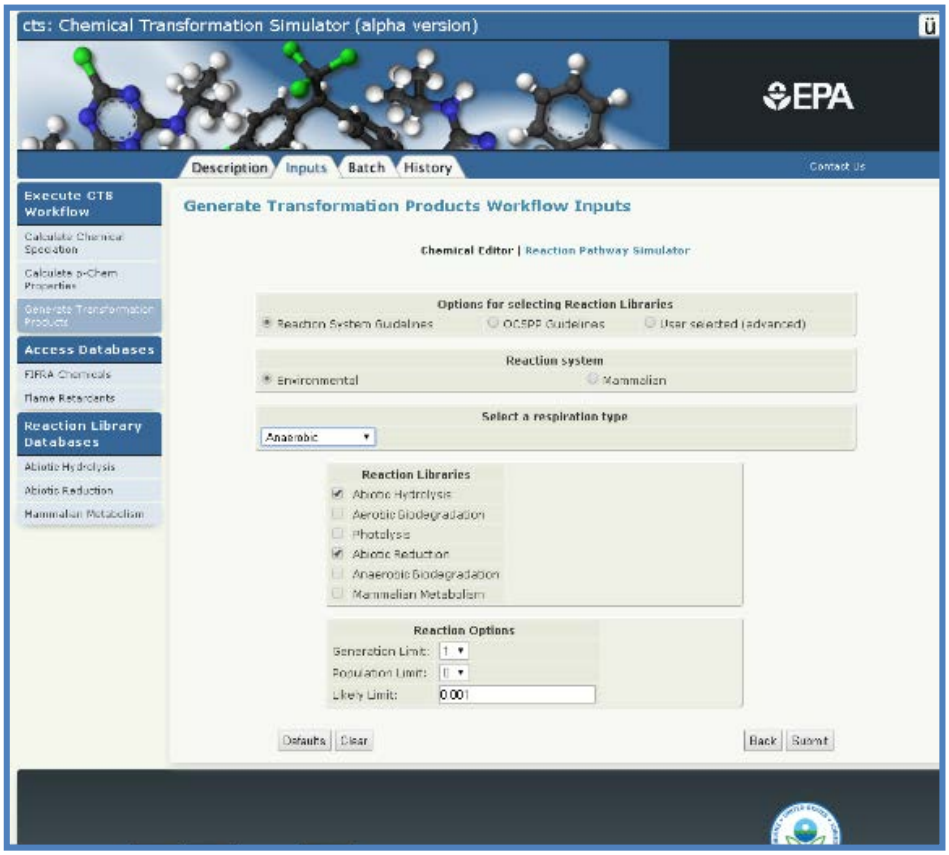


Figure 20

Selection of aerobic respiration opens the window with the reactions libraries that are currently available and will potentially occur under these conditions, which currently includes only abiotic hydrolysis.

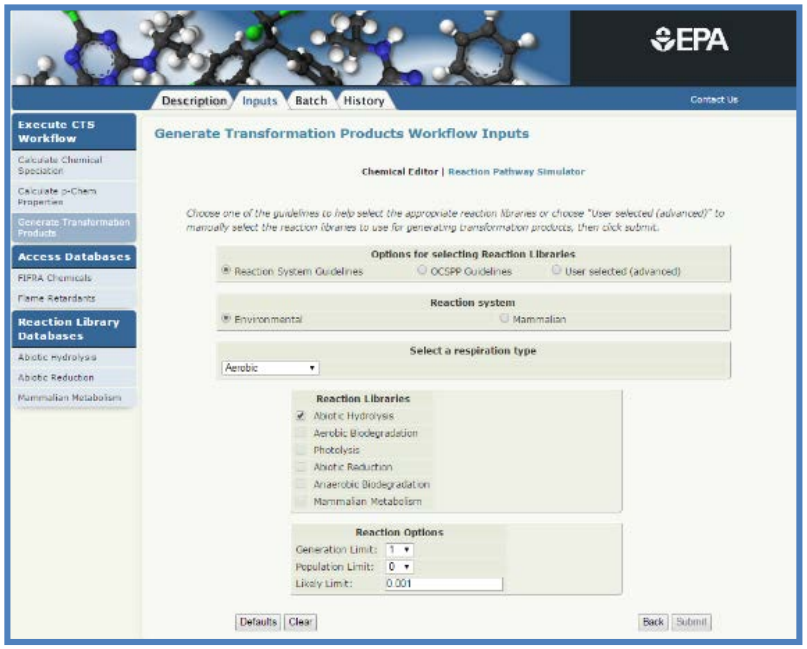


Figure 21

Selection of mammalian reaction systems opens the window with the mammalian reactions library selected. This is the only option available for the mammalian reaction system.

Figure 21

The second option for the selection of reaction libraries is through the selection of the OCSPP s Fate, Transport, and Transformation (Series 835) or Health Effects (Series 870).

Selection of the Fate, Transformation Series provides the user with three options:

- Laboratory Abiotic Transformation Test Guidelines
- Transformation in Water and Soil Test Guidelines
- Transformation Chemical-Specific Test Guidelines

As an example, selection of the Laboratory Abiotic Transformation Test Guidelines shows that both the abiotic hydrolysis and abiotic reduction are appropriate selections for this option.

Figure 22

Selection of Health Effects provides the user with one option for selection of a reaction library (i.e., mammalian metabolism).

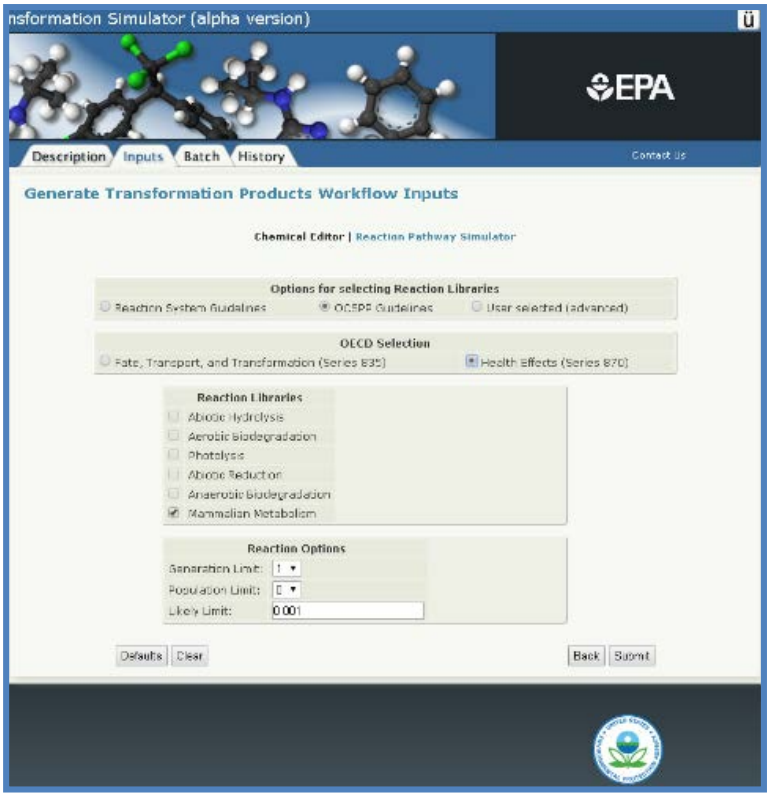


Figure 23

The third option for the selection of reaction libraries is through the selection of the User Selected, which is considered to be an option for the more advanced user. This option provides the user with the ability to select amongst the currently available reaction libraries including abiotic hydrolysis, abiotic reduction and mammalian metabolism.

Figure 24

As shown below, the user has the option of selecting more than one reaction library.

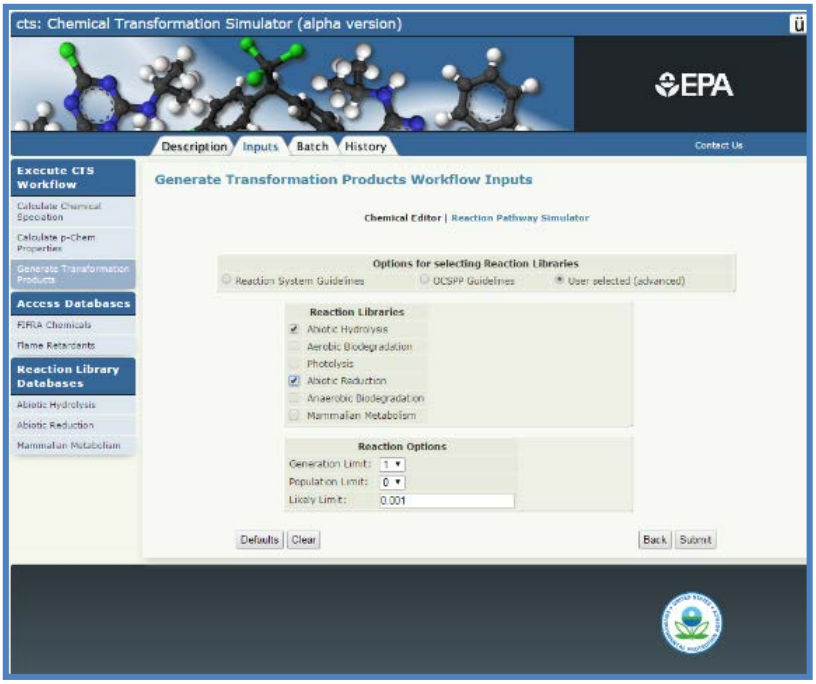


Figure 25

After selecting the reaction libraries, through one of the three options; the user is given the option to change the Reaction Options, including the:

- **Generation Limit:** the maximum number of generations of transformation products that will be generated
- **Population limit:** the maximum number of products that can be formed in one generation (currently not functional)
- **Likely Limit:** limits the global accumulation of products based on likelihood values (currently not functional)

After selecting the reaction libraries and reaction options, the user clicks the submit key to generate transformation products. The results screen summarizes the input data and provides the 1st generation of transformation products (the default value), based on the execution of the abiotic hydrolysis and reduction libraries. The user can expand the number of viewed generations using the drop down at the top left hand corner of the reaction pathway map. The screen on the right below illustrates the reaction pathway map for the formation of two generations of products. Note that the number of observed generations cannot exceed the Generation Limit set by the user on the previous screen. By highlighting a product with the cursor, a number appears that signifies its place in the reaction pathway map. For this example, tetrachloroethene (1.2.2) is the 2nd product formed in the third generation from the 2nd product (i.e., pentachloroethane), which was formed in the second generation from hexachloroethane.

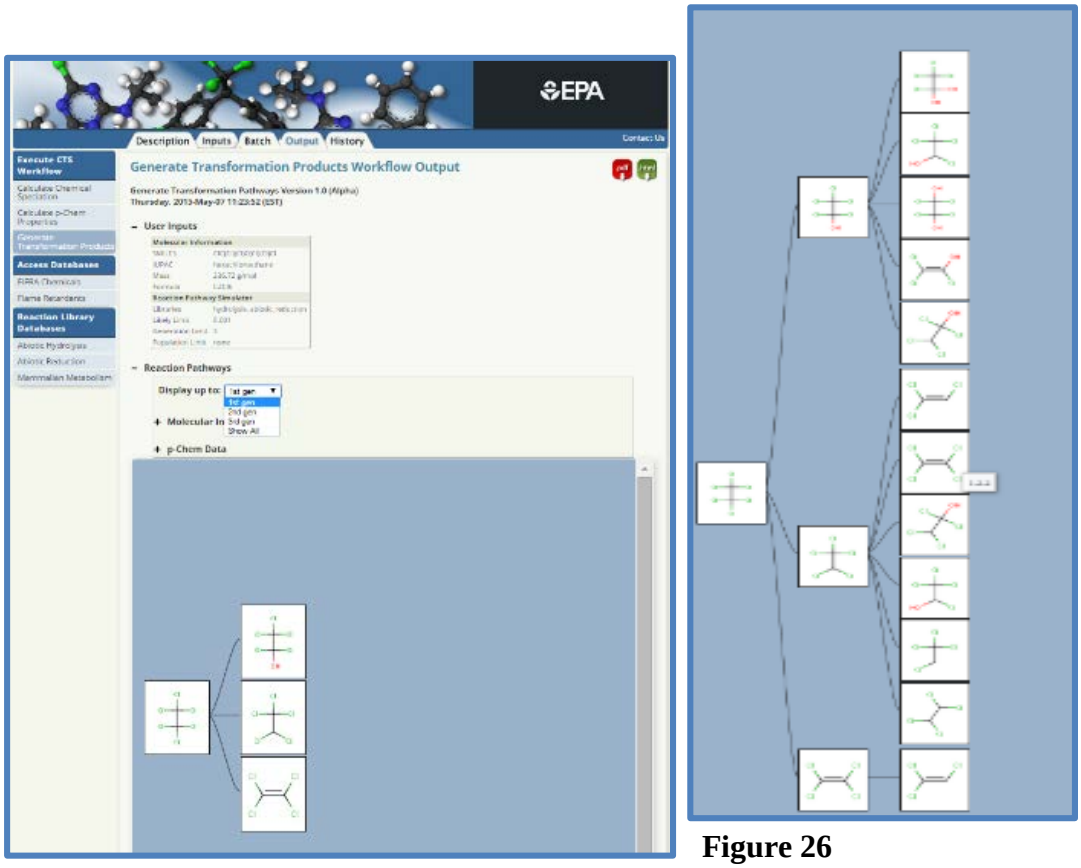


Figure 26

The user also has the ability to display the 2nd generation of transformation products for a given transformation in the 1st generation, by manually left clicking on that product. For this example, tetrachloroethylene was selected to show the 2nd generation product trichloroethylene.

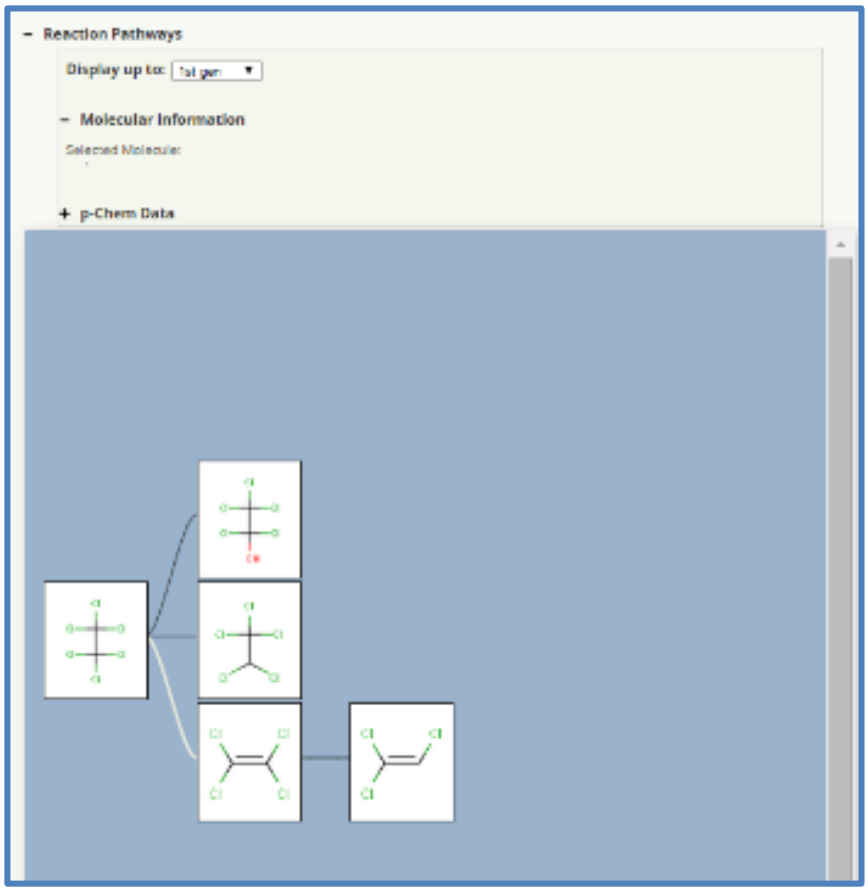


Figure 27

The user can right click on any of the structures in the reaction pathway map to generate the molecular information for the selected chemical. For the example below, this information is illustrated for pentachloroethanol.

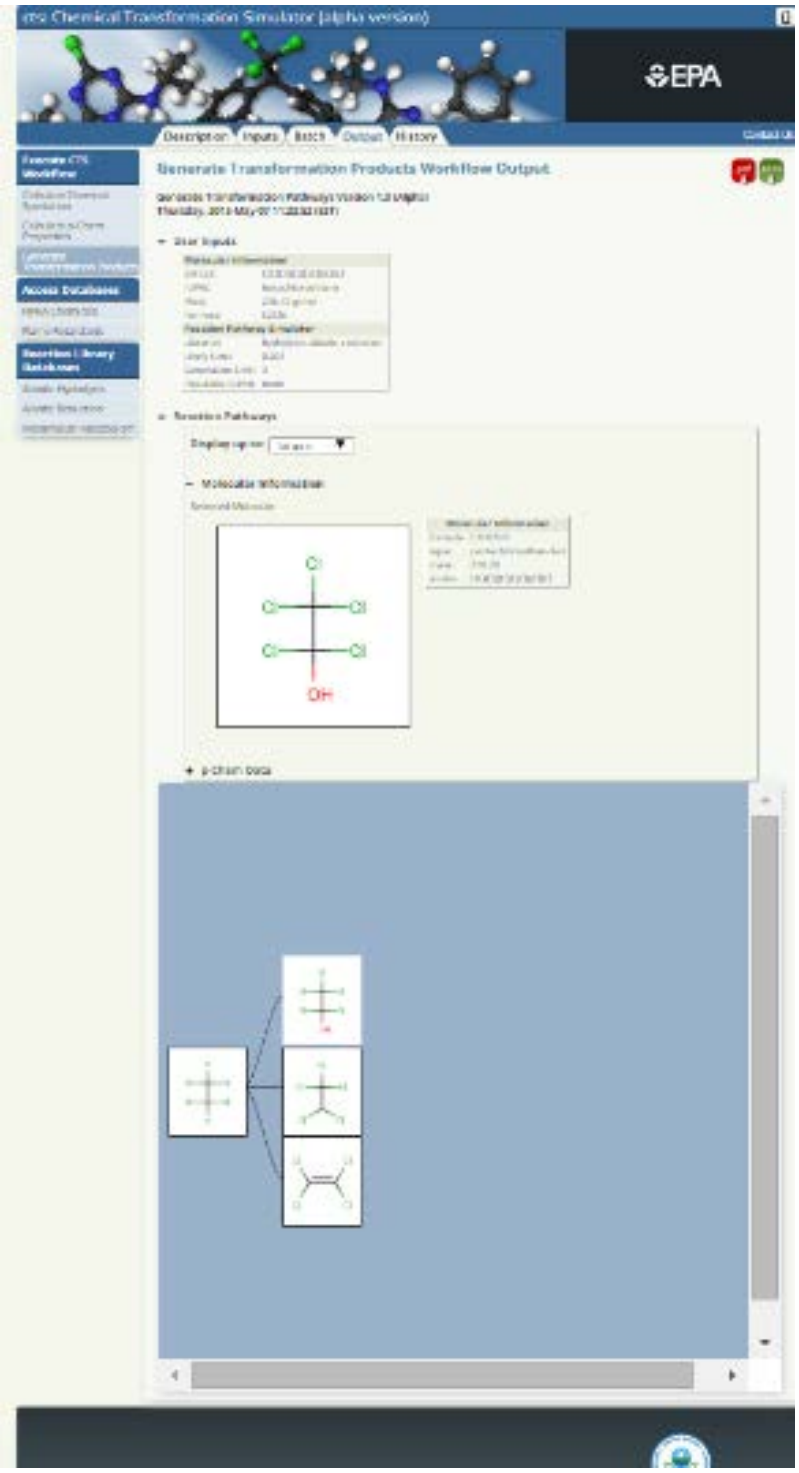


Figure 28

Selection of the p-Chem Data tab under Reaction Pathways provides the various options for p-chem properties and calculators to be applied to the selected transformation product. (See the screen below on the left side.) P-chem properties will be calculated and displayed in the selection table. For example, clicking the the All and ChemAxon buttons and then clicking the get data button provides the screen below on the right side, showing the results for the ChemAxon p-chem calculator for pentachloroethanol. If multiple products are selected, the results are not shown in the data table. Users could view the results but can be viewed in the pdf file, which is generated by clicking on the .pdf button.

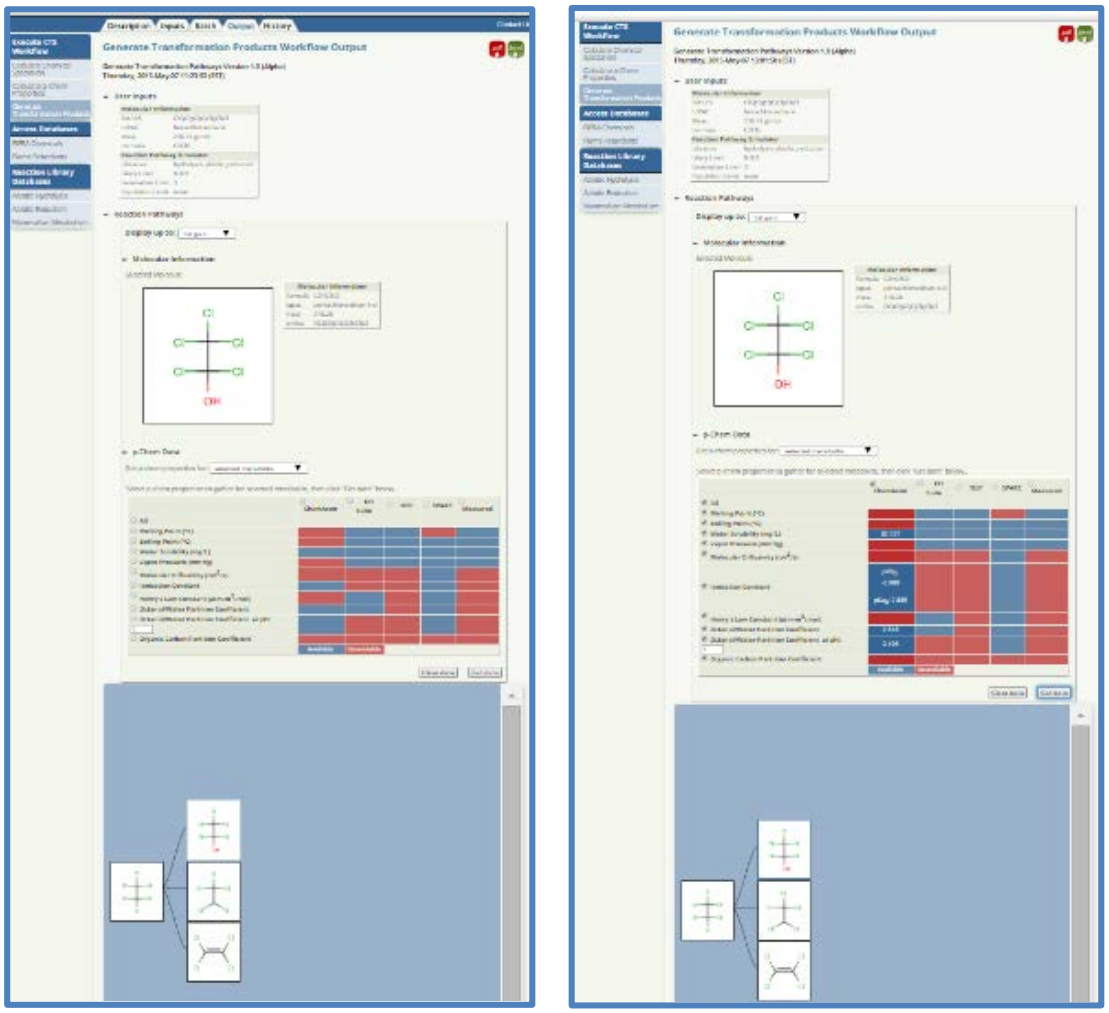


Figure 29